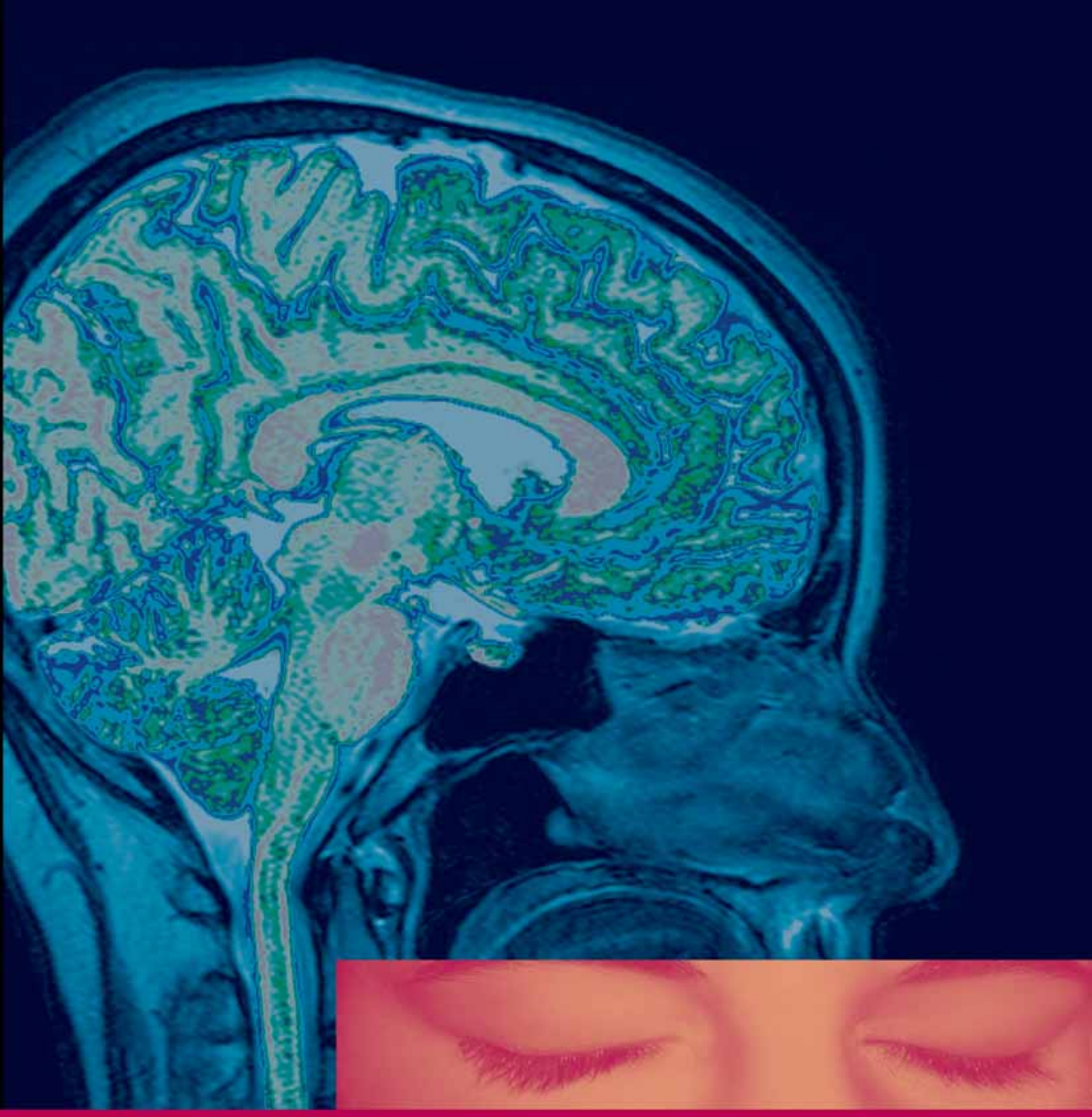

Clinical Pharmacology of Sleep

S.R. Pandi-Perumal and J.M. Monti (Editors)

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Clinical Pharmacology of Sleep

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Foreword

From the emergence of clinical sleep medicine marked by the establishment of the harbinger Stanford Sleep Disorders Clinic in the mid 1970s, offspring sleep disorders clinics and centers have grown exponentially with the recognition of the unmet diagnostic and treatment needs of the reservoir of patients suffering from symptoms of what are now recognized and classified as the nosology of human sleep disorders. Important in the growing armamentarium of treatment options for the sleep practitioner are both traditional and newer pharmacological agents, including over-the-counter, non-traditional, and prescription types, that are all used to treat, sometimes adjunctively, most clinically recognized sleep disorders.

Although there are numerous academic treatises and reviews dealing with individual treatment alternatives for the diversity of recognized sleep disorders, no one comprehensive resource, extant, has dealt with pharmacological treatment options and strategies for the major human sleep disorders associated with a panoply of symptomatic conditions. The present volume and its series of chapters individually focusing on a range of human conditions, from pediatric sleep disorders to sleep-related disorders of individuals suffering from Alzheimer's dementia, uniquely cover the wide range of human medical conditions amenable to thoughtfully sleep-related applied drug therapy.

The Editors have brought together a superb group of internationally respected sleep clinicians, and researchers, that provide state-of-the-art analysis of the current basic and clinical perspective regarding the most common sleep disorders that are amenable to pharmacological treatment. In each chapter the authors outline a thorough historical background of the particular disorder and review the basic pre-clinical studies leading to current treatment options.

Readers can pick from chapters regarding clinical conditions for which they have particular interest or can quickly scan chapters to bring themselves up to date about the most current views regarding treatment options in a variety of human conditions with particular sleep-related symptomatologies. Overlapping material occasionally occurs between various chapters but this poses no real concern as it is unlikely that individual readers will read straight through all the chapters, this being a review volume. Readers will have a tendency to pick and choose their clinical subject matter as it relates to their interest in specific conditions and their clinical pharmacology.

Clinical Pharmacology of Sleep is an important and timely monograph dealing with the second or third generation pharmacological treatment strategies available to the sleep disorders practitioner. Undoubtedly, these strategies will further evolve over

time with the development of more targeted pharmacological agents or combinations of drugs based on both preclinical and well as more controlled clinical trials and studies. Until then, this volume brings together the extant state-of-the-art information that will help sleep professionals as well as interested neuroscientists and, indeed, the lay public interested the evolving pharmacology of sleep and its disorders.

Steven Henriksen, PhD
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October, 2005

Preface

During the past decades, sleep research has seen enormous progress. Numerous discoveries have been described in a wealth of papers of ever increasing size and complexity. These publications have become difficult to follow not only because of their number, but also because they have been published specialty journals that are not easily accessible.

The clinical pharmacology of sleep is a fascinating field of medical science. Its subject matter touches all facets of our health and well being. Additionally it is becoming a highly interdisciplinary field. We have striven to present chapters, which hopefully will make the reader's experience both enjoyable as well as meaningful.

This book is intended primarily for sleep researchers, general- and neuropharmacologists, psychiatrists, and physicians who evaluate and treat sleep disorders. In addition, the volume will be useful to pharmacologists, pharmacists, medical students and clinicians of various disciplines who want to get an overall grasp of the clinical pharmacology of sleep.

This volume includes contributions from a wide range of authors, many of whom are world-recognized authorities in their field. Chapters in this volume deal with a range of topics, including, among others, the pharmacological treatment of insomnia, sleep disturbance in anxiety disorders, benzodiazepine and non-benzodiazepine hypnotics and their molecular pharmacology, rebound and withdrawal effects, and chronopharmacology and its implications for the pharmacology of sleep. A wide range of new drugs and pharmacological concepts are discussed in the volume. The reader may feel confident that the information presented is based on the most recent sleep pharmacology literature. Furthermore, the importance of this information to medicine and therapeutics is stressed.

This book will explore many of these new and exciting developments. Unfortunately, it is impossible in a book such as this to include all recent advances, but that is what makes Clinical pharmacology such an exciting field to explore.

It has been the intention of the editors to provide in this volume a comprehensive and up-to-date coverage of specialized topics in the clinical pharmacology of sleep. It is our hope that we have succeeded in accomplishing this goal.

The editors and authors would appreciate feedback on the contents of the book with particular regard to omissions and inaccuracies.

New York/Montevideo, July 2005

S.R. Pandi-Perumal
J.M. Monti

Credits and acknowledgements

An enterprise of this sort is bound to be contentious and challenging, and editors who attempt such things need all the help they can get. Several people were instrumental in the production of this new volume of *Clinical Pharmacology of Sleep*.

The dedicated staff of Birkhauser-Verlag, Basel, Switzerland made this project an especially pleasurable one. In particular we wish to acknowledge the invaluable help of Dr. Beatrice Menz, senior editor – Bioscience division, who supported from the start to finish and has provided simply an outstanding editorial management throughout this long process, and we are deeply in her debt.

We thank the team members for their dedicated efforts in helping us to complete our project in a timely manner and making editorial contributions, to whom we offer our hearty thanks. A very special debt of gratitude and appreciation is owed to the several reviewers who made numerous helpful suggestions. Their candid comments and insights were invaluable.

To all the people who contributed to this project, we want to say 'thank you'. Their willingness to contribute their time and expertise made this work possible, and it is to them that the greatest thanks are due. They make our work possible and enjoyable.

Without a whole host of dedicated people, this volume would never have come to completion. All of the above experts made this book possible. We recognize them individually and collectively for their contribution.

Finally, on a personal note, the editors as individual would like to acknowledge the close co-operation we have received from each other. We think that we made a good team, even if we say it ourselves!

Last, but certainly not least, we owe everything to our wonderful wives and families. Without the love and support of our families and friends we could not have completed this project. They saw the work through from conception to completion with unwavering optimism and encouragement. You are the source of joy and inspiration for us – thank you for your continual support, and for understanding the realities of academic life!

Dedication

To our wives and families,
who are the reasons for any of our accomplishments
who have taught and aided us
In much of what we know and do

Two are better than one,
because they have a good reward for their labor.
For if they fall, one will lift up his companion,
but woe to him who is alone when he falls,
for he has no one to help him up.

– Ecclesiastes 4:9

Clinical Pharmacology of Sleep
Edited by S.R. Pandi-Perumal and J.M. Monti

Primary and secondary insomnia

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Introduction

Insomnia is a serious health problem. With an estimated 30 000 000 Americans experiencing chronic, clinically significant insomnia [1], this condition is the most prevalent sleep disorder and is among the most prevalent psychiatric disorders. The health burden of insomnia is felt in a number of ways. It has an estimated annual economic impact in the United States alone of about $ 14 billion as of 10 years ago [2]. Not only is nighttime experience degraded, but quality of life, broadly conceived, is also compromised [3].

Chronic insomnia compounds its initial impact with long-term health consequences. It is a health risk factor for a number of disorders including anxiety, depression, and substance abuse/relapse [4]. Serious iatrogenic effects may afflict a significant percentage of those individuals who seek relief through hypnotics. In this subgroup, there is heightened risk of automobile accidents [5] and hip fractures [6], with the greatest vulnerability occurring among older adults consuming long half-life benzodiazepines.

The remainder of this chapter discusses the characteristics of primary insomnia (PI) and secondary insomnia (SI). Each of these two sections is structured to cover prevalence, causes, and diagnosis.

Primary insomnia

PI is a disorder characterized by difficulty initiating and/or maintaining sleep. It is distinguished by its etiological independence from other physical or mental disorders.

Prevalence

The high prevalence of insomnia is well documented. One national phone survey estimated that 9 % of the population reported difficulties sleeping on a consistent basis, and 27 % indicated occasional sleeping problems [7]. A large survey-based

epidemiological study conducted in France [8] found that 19 % of the population met criteria for insomnia as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [9]. Another recent study assessed the sleep of 772 individuals using 2 weeks of sleep diaries and found that 16 % of individuals reported consistent sleeping problems for at least 6 months, including reported daytime impairment [1].

The prevalence studies noted above only consider the general population without regard for differences between specific groups. Research has identified many characteristics that may influence the frequency/severity of insomnia complaints including age, gender, socioeconomic status, and ethnicity.

It is well documented that insomnia complaints increase with age, and women complain more about insomnia than do men. Lichstein et al. [1] reviewed 20 studies that included diverse age groups, and in 13 investigations, insomnia complaints increased with age. The median prevalence rate across all studies was 15 %, compared to 25 % among older adults. Lichstein et al. [1] also summarized 33 studies that reported gender differences in sleeping difficulties. No study found increased insomnia prevalence among men, eight studies observed no differences between men and women, and 24 studies found higher insomnia prevalence among women. The median prevalence rate across all studies was 12 % for men and 18 % for women.

Evidence is accumulating that suggests a higher prevalence among individuals in lower socioeconomic status (SES) brackets. Increased reports of insomnia complaints were found among unemployed individuals [10], people with less income [11], and individuals with fewer years of education [11, 12].

Studies have also shown a higher prevalence of sleeping difficulties among African-American adults compared to Caucasians [13], greater severity of insomnia among African-American adults compared to Caucasians [1], and polysomnography (PSG) studies of normal sleepers suggest that African-American adults experience less deep sleep than Caucasians [14, 15]. It should be noted that existing studies suggest that among older adults, African Americans are less likely to experience poor sleep [1, 16, 17].

Causes

PI is thought to derive from numerous factors, but primarily these are physiological, cognitive, and behavioral.

Physiological model

The physiological model assumes that people with insomnia (PWI) have a predisposition to experience high levels of arousal, which is incompatible with sleep onset and sleep maintenance. Numerous investigations have found increased physiological arousal in PWI as compared with people not having insomnia (PNI) across a variety of arousal measures [18–22]. These findings have since been replicated assessing throughout the entire 24-hour period [23].

This model is also consistent with evidence regarding objective measurements of daytime sleepiness in PWI. Numerous studies have demonstrated that sleep-deprived PWI, who report subjective daytime sleepiness, nevertheless show equal or longer

delay in falling asleep during daytime nap tests, as compared to PNI [3]. Although these studies may suggest that PWI are not as sleepy as their self-report would indicate, it is plausible that the same mechanism (presumably increased arousal) that obstructs sleep in PWI during the night also contributes to the inability to initiate sleep during the day.

Cognitive model

Much evidence exists that PWI report difficulty turning off their minds at bedtime [24, 25]. Pre-sleep thought content seems to involve worry and concern, particularly about the inability to sleep [26]. PWI also tend to catastrophize about the consequences of insomnia and to maintain unrealistic expectations about their sleep requirements [27]. A recent model of insomnia [28] detailed ways in which cognitive factors may perpetuate sleeping difficulties. This model contends that catastrophizing thoughts about the inability to sleep will increase anxiety about initiating sleep. Excessive anxiety, in turn, results in biases in attention and greater focus on being awake and, consequently, in an overestimation of awake time during the night. Additionally, excessive anxiety about daytime consequences of insomnia will lead to biases in attention that confirm the perception of being more sleepy and fatigued. These events serve to increase nighttime worry and further decrease sleep propensity.

Behavioral models

Behaviors that may influence sleep contribute to two separate causal models: stimulus control and sleep hygiene.

According to the stimulus control paradigm, insomnia is a learned behavior due to associating the bed and the bedroom with incompatible sleeping behaviors. Through the course of spending too much time in bed when not sleeping, the stimulus (in this case, the bedroom) elicits multiple responses other than the desired response of sleep [29]. For instance, the bed and bedtime may trigger thoughts that are incompatible with sleep, such as planning for the next day, rehashing of the day's events, worrying about life concerns, or worrying about not being able to fall asleep. Although this paradigm has not been empirically validated, evidence for its usefulness derives from the effectiveness of stimulus control treatment, which works to eliminate sleep incompatible responses elicited by the bedroom.

Sleep hygiene broadly refers to a set of behaviors that influence the quality of one's sleep, and good sleep hygiene entails practicing behaviors that contribute to good sleep, while avoiding behaviors that disturb sleep [30]. Sleep may be negatively affected by a number of specific behaviors, including drinking caffeinated beverages, smoking, drinking alcoholic beverages, exercising too close to bedtime, and maintaining an inconsistent sleep schedule [31, 32]. One study calculated the frequency of diagnoses listed in the International Classification of Sleep Disorders: Diagnostic and Coding Manual (ICSD) [33] of patients presenting in sleep clinics, and found that in 6.2 % of those individuals the sleep problem was primarily due to inadequate sleep hygiene, and sleep hygiene contributed to sleeping problems in 34.2 % of the patients [34].

Diathesis-stress model

A multi-factor model [35] contends that individuals may be predisposed to experience sleeping difficulties, and behaviors or life events may trigger this tendency. This model also posits that poor sleep habits may perpetuate initial sleeping difficulties, and increase the likelihood of chronic insomnia. Predispositions for insomnia have been attributed to factors such as hyperarousal [23] and increased tendency to worry or ruminate [36, 37]. These predispositions, in turn, increase the likelihood that sleeping patterns will be disturbed, given the presence of increased psychological or somatic distress, or poor sleep hygiene. Furthermore, this model contends that early symptoms of insomnia may lead to the stimulus control problem of spending too much time in bed without sleeping, thus increasing the possibility of chronic insomnia.

Diagnosis

There are two major diagnostic manuals that provide classification systems for sleep disorders and define criteria for insomnia conditions: the DSM-IV and the ICSD. Both manuals employ different terminology to label insomnia conditions, and present varying ways to define insomnia.

The DSM-IV is the only diagnostic manual that uses the term 'Primary insomnia', and this disorder requires three characteristics: (1) poor sleep for at least 1 month, (2) the sleep disturbance causes clinically significant daytime impairment, and (3) this problem cannot be better explained by another mental or physical condition, or substance use. The ICSD classifies sleeping disorders according to the presumed cause of the condition, and consistent with DSM-IV criteria, all ICSD insomnia-related disorders require a complaint of insomnia and associated impaired daytime functioning. Two ICSD disorders may be subsumed under the DSM-IV notion of PI: psychophysiological insomnia and idiopathic insomnia. In the case of psychophysiological insomnia, evidence is required that relates the problem of insomnia to either somatized tension or learned sleep-preventing associations. Idiopathic insomnia refers to a lifelong pattern of poor sleep that presumably has neurological substrates. The ICSD also presents criteria that separate PWI by the duration of their symptoms. 'Chronic insomnia' refers to symptoms that persist nightly for at least 6 months. 'Subacute insomnia' is characterized by symptoms that appear for more than 1 month and less than 6 months, and 'Acute insomnia' describes symptoms have existed for less than 1 month.

These two diagnostic systems do not set frequency or severity criteria, and the ultimate decision in conferring the insomnia diagnosis rests on clinical judgment, but progress has occurred in establishing quantitative criteria. Based on modal research practice and the sensitivity-specificity profile [38], the following quantitative criteria for insomnia can be justified: sleep latency or awake time during the night for 31 min or longer, occurring at least three times per week, and lasting 6 months.

Secondary insomnia

SI is the term given to cases of insomnia that appear to be secondary to other distressful conditions or secondary to substance use. 'Secondary' in this context means that another condition causes and maintains the insomnia. Insomnia cases where no causal link exists, but where insomnia and another condition co-occur yet function independently, are referred to as 'co-morbid'. If an insomnia state is clearly secondary to another condition, then presumably, the insomnia will subside if the primary condition is successfully treated, but data to support this SI conceptual scheme are scarce, calling into question the concept of causal influence in supposed SI.

Prevalence

By clinical presentation, the majority of insomnia cases appear to be secondary to either mental or physical disorders, but specific rates are difficult to establish. Often epidemiological studies do not specify type of insomnia, and the ones that do rarely differentiate SI from co-morbid insomnia [39]. A number of studies indicate rates of co-morbid insomnia with another mental disorder, rates which vary (below 10 % to above 80 %) according to the criteria used to evaluate insomnia [40]. Some studies survey rates of complaints of insomnia, while others use diagnostic criteria and structured interviews. An epidemiological study of psychiatric disorders and sleep disturbances [10] found a 50 % rate of co-morbidity between insomnia and psychiatric conditions. Furthermore, a review of diagnostic data from six sleep disorders centers [41] revealed a 75 % rate of SI among insomnia patients. Ohayon's [42] epidemiological study, which used the most thorough interviews to date, found the rate of SI to be around 65 % of those who had insomnia (51.8 % secondary to a psychiatric disorder, 8.9 % secondary to a medical disorder, and 3.6 % secondary to substance use). This study also revealed that insomnia secondary to a medical condition is more prevalent in older adults than middle-aged adults (9 to 1) but found insomnia secondary to a psychiatric condition more common in younger individuals.

Causes

SI may be caused by a number of physical conditions including asthma, fibromyalgia, chronic fatigue syndrome, pulmonary disease, gastroesophageal reflux, renal failure, headaches, heart disease, arthritis, Parkinson's disease, Alzheimer's disease, and Huntington's disease [41]. Other sources of SI are psychiatric disorders and substances. Mental disorders which can cause insomnia include anxiety disorders, many types of drug withdrawal, major depressive disorder, and dysthymic disorder [40]. A primary disorder can instigate SI through a direct neurological link such as muscle tremors, through pain, or through stress [41]. Furthermore, many of the instigators of insomnia are also reactive to insomnia. For example, studies have shown that insomnia is both caused by and exacerbates headaches and other types of pain [43, 44].

Common, non-prescription substances such as caffeine, nicotine, and alcohol often cause sleeping difficulties [41]. In addition, a number of prescribed medications and illegal substances can cause insomnia, depending on factors such as amount used, time of usage, and individual response. Types of drugs that can cause insomnia include energizing antidepressants, anti-hypertensives, bronchodilators, diuretics, beta-blockers, and corticosteroids.

It is important to remember that no medical or mental condition universally causes insomnia [45]. Similarly, not all medications within the classes associated with insomnia contribute to sleeping problems in all people [41].

Diagnosis

The DSM-IV names three types of SI: insomnia arising from a primary mental disorder, insomnia arising from a medical condition, and insomnia arising from a substance. The manual lacks criteria for determining the secondary nature of the insomnia, merely indicating that one should identify a relationship between the onset, exacerbation, or remission of the condition and the onset, exacerbation, or remission of the sleep disturbance, but without suggesting any method for determining this association. DSM-IV also mentions that substance-induced insomnia could arise from prescription or illegal substances, and suggests that establishing a rationale for how the condition or substance could cause the insomnia strengthens the diagnosis of SI.

The ICSD similarly conceptualizes SI and is similarly lacking in methods for determining causality. It lists 19 medical and psychiatric conditions and substances that may plausibly cause insomnia, and calls for a temporal connection to be observed between the condition or substance and the insomnia.

The necessary component for an SI diagnosis arising from these two classification systems is strong evidence for a causal relationship, serving to rule out co-morbidity, and serving to rule out misattribution of the "primary condition" [41]. This evidence comes in the forms of a causal rationale and of a correlational history indicating a temporal sequence compatible with the claim that the condition or substance causes the insomnia. The interrelated careers of the insomnia and the primary condition provide the main basis on which the SI diagnosis is built, and these types of correlational data become increasingly unreliable with the longevity of the insomnia.

Lichstein [41] conceptualized three types of SI that highlight diagnostic complexities. 'Absolute SI' is the type of SI in which the insomnia is completely dependent on the primary condition, such that insomnia onset occurred shortly after the onset of the primary condition and such that any variation in frequency, duration, or severity of the primary condition results in a similar variation for the insomnia. However, there may be times when insomnia exists before the onset of another condition and is worsened by the other condition. Likewise, there are cases when a primary condition causes insomnia, but, over time, the influence of the primary condition fades and the insomnia evolves into an independent condition. Either way, these cases in which the insomnia is partially dependent on and partially independent of the other condition characterize what Lichstein referred to as 'partial SI'. Finally, 'specious

SI' characterizes the false positive, when the diagnosis of SI is given due to a temporal sequence and a rationale consistent with causality when, in fact, no causality exists. Lichstein's conceptualization of SI points to the high degree of difficulty for accurately diagnosing SI. Clinicians can merely provide an educated guess about the causal relationship, one that commonly relies heavily on the memory of the patient. The only study investigating the reliability of diagnosing SI found it to be poor, $\kappa = 0.42$ [46]. The diagnosis of SI is inferential rather than definitive; and the presence of SI does not rule out PI, as these two types of insomnia can exist simultaneously.

To reduce the mystery of this far-reaching sleep problem, we dissect insomnia and, then, create categories within its spectrum according to a myriad of causes. Although we understand the theoretical differences between PI and SI, and between SI and co-morbid insomnia, identifying these insomnia subtypes is achieved with a skeleton of science and a bulk of clinical judgment. The reality, that we never really know whether we are treating SI, PI, or co-morbid insomnia, should, at least, cause clinicians to second-guess as much as they guess about causality, throughout this diagnostic process.

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Primary insomnia: diagnosis and treatment

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Introduction

Insomnia is a quite prevalent condition in the general population; its documented prevalence is rather variable, however, raging from 10 % to 48 % [1]. This impressive variance may be related to a number of reasons. It may reflect methodological differences across studies regarding either sample characteristics or means of investigation (questionnaires, telephone surveys, interviews) [1, 2]. Most likely, however, it may originate from differences relating to the definition of insomnia. Thus, in some studies the decision of who is an insomniac is based on the detection of reduced sleep quantity (difficulty falling asleep, difficulty staying asleep and/or inadequate total sleep time), while in others it relies on the presence of poor sleep quality [1]. Also, an important source of variance is the different time frame utilized in various studies for the assessment of sleep difficulty, e.g. , "now", "2 weeks or more", "last month", "last year", "last 18 months" [1]. Similar differences are found even among current classification systems in terms of their proposed diagnostic criteria for insomnia [3–5]. The International Classification of Diseases -10 (ICD-10) provides both a frequency criterion (at least three times per week), and a duration criterion (at least 1 month), while International Classification of Sleep Disorders (ICSD) contains only a frequency criterion (nightly) and Diagnostic and Statistical Manual of Mental Disorders (DSM IV) only a duration criterion (at least 1 month).

Progressive inactivity, dissatisfaction with social life, and presence of medical and psychiatric illness can be most predictive of insomnia in old age [6, 7]. In modern societies higher rates of insomnia are present in women, people who are less educated or unemployed, separated or divorced, the medically ill, and those with depression, anxiety, or substance abuse [8]. In a number of studies, insomnia has been found to be correlated with frequent use of medical facilities [9–13], chronic health problems [13–18], perceived poor health [17], increased use of drugs [10, 14], and specific medical conditions including respiratory diseases [19–21], hypertension [21], musculoskeletal and other painful disorders [19–24], heart diseases [19, 23], and prostate problems [19]. On the other hand, chronic insomnia predisposes to the development of psychiatric disorders [25–27]. Therefore, it is important to clearly establish whether co-morbidities are causative for, or simply co-exist with insomnia, in order to recommend the most appropriate treatment. This is why it is better to categorize insomnia as a disease rather than as a symptom [28].

Individuals with sleep disorders have great impairment in the quality of their life [9, 12, 29]. Furthermore, another important aspect related to the high prevalence of insomnia is its economic cost for the health care services. This not only includes the direct costs of diagnosis and treatment (including also the over-the-counter drugs, and the cost of the associated alcoholism), but in addition the substantial indirect costs related to absenteeism, diminished productivity, accidents, and other health problems that are secondary to insomnia [30–32].

Diagnosis of insomnia

The diagnostic criteria for insomnia can indeed become very precise. Insomnia in the ICSD [3] was defined as "the complaint of an insufficient amount of sleep or not feeling rested after the habitual sleep episode", which might denote that sleep quantity and quality should be considered as equivalent. However, there were actually two quantitative requirements in ICSD for the diagnosis of insomnia: at least 20 min sleep latency and at the most 6.5 hours total sleep time, otherwise the condition was considered as "sleep state misperception" also called "pseudoinsomnia" [3].

According to ICD-10 [4], the sleep disturbance must have occurred at least three times per week for at least 1 month. The 1-month timeframe is essential also for primary insomnia in the American Psychiatric Association's DSM-IV classification [5]. Also the patient must complain either of difficulty falling asleep or maintaining sleep, or of poor quality of sleep. However, the presence of the complaint of unsatisfactory sleep is not sufficient for the diagnosis of insomnia in its own right. It should also be a source of marked distress for the patient, and it should interfere with his/her ordinary activities in daily living. This prevents mistaking insomnia for just a symptom of another mental or physical disorder.

Following publication of the ICD-10 diagnostic criteria for insomnia, which are quite similar to those of DSM-IV, the Athens Insomnia Scale (AIS) was developed with the main goal of assisting clinicians in diagnosing insomnia on the basis of ICD-10 [33, 34]. However, while the diagnostic criteria concerning time, so that a sleep disturbance may be diagnosed as insomnia, are precise and of clinical value, what is also required is the subjective feeling of discontent [33, 34]. This means that the patient should report dissatisfaction concerning the amount and even the quality of his or her sleep. What is notable is that most people suffering from insomnia say they do not feel refreshed when awakened. Thus, sleep in insomniacs does not fulfill the task of rest and relaxation, for both the body and the mind.

The main factor, leading most patients to develop chronic insomnia is hyperarousal. These people develop high levels of arousal, either due to their personality, or because they are going through a stage where they cannot effectively manage their everyday stress. Indeed, quantitative electroencephalogram analysis in patients suffering from insomnia, indicates an increase in beta frequencies at sleep onset and during non-rapid eye movement (REM) sleep, reflecting an increased thinking process, or hyperarousal of the brain [35, 36]. What is also very common is the emergence of thoughts virtually suspending the onset of sleep. This means that a person

suffering from insomnia is worried that he or she would not be able to manage to fall asleep, when the time to go to bed comes [37]. The person is thus becoming stressed and finds it hard to relax. Not rarely patients are feeling like convicts, when going to bed. They consider bed as a place of torture and become discontent just by thinking of it. A term suitable for describing such thoughts is 'learned sleep-preventing associations'.

In an attempt to document hyperarousal in patients suffering from insomnia, functional neuroimaging methods, assessing regional cerebral glucose metabolism were used [38]. Evidently, subjectively disturbed sleep was associated with greater brain metabolism. Thus, it is possible that the inability to fall asleep is related to a failure of arousal mechanisms to decline in activity from waking to sleep states. This may be an explanation why there is an association between chronic insomnia and alcohol dependence [39]. Perhaps some individuals with hyperarousal and failure in their mechanisms to control it, try self-treatment methods through alcohol consumption.

In a recent study of a large group of people, representative of seven European countries, about 11 % complained of nonrestorative sleep [40]. The complaints concerning nonrestorative sleep are indicative of hyperarousal not allowing relaxation during sleep. Nonrestorative sleep was associated with the presence of anxiety, and stressful life. Furthermore, the prevalence was higher in the United Kingdom (16.1 %), and Germany (15.5 %), than in Spain (2.4 %). By these findings one may conclude that the more society is following the modern western pattern of life, the harder the stress management becomes, and consequently sleep disturbances become more common.

Indeed, in a survey of Japanese white-collar male daytime workers, psychological job stress factors, job satisfaction, and social support were independently associated with a modestly increased risk of insomnia [41]. Furthermore, in a population of employees with no reported sleeping problems, 14.3 % developed a sleeping problem during the following year. Stress in the form of a "poor" psychosocial work environment doubled the risk of developing a sleep problem [42].

Regarding the environmental conditions, which provide a good shelter to the individual during his/her sleep, little is known about the relationship between the occurrence of sleep disturbances and the home environment. However, recently, it has been documented that insomnia is more common in subjects living in damp buildings [43], which means that even a limited annoyance may affect sleep and produce chronic insomnia.

Insomnia in general, defined by difficulty in falling asleep or remaining asleep, early morning awaking and/or nonrestorative sleep, is an important public health issue. It has significant negative impact on individual physical and social performance, ability to work and quality of life [28], and, although chronic insomnia warrants treatment, in the majority of cases is often under-treated [28]. Traditional epidemiological studies of insomnia provide valid but fairly rudimentary information regarding the presence, frequency, duration and evolution of sleep problems [44]. Polysomnography provides an accurate measure of sleep latency and total sleep time, but it is a very expensive approach, and does not address the issue of poor quality of sleep. On

the other hand the use of a daily sleep diary, although it is a useful tool for evaluating sleep in the patient's home environment [45], it not an objective means of assessment. Actigraphy is an alternative assessment, using a small watch-like device, which could provide objective data that would be combined with those obtained through a sleep diary [46].

Standardized tools such as validated questionnaires (e.g. , Pittsburgh Sleep Quality Index, or AIS [33, 47]) help assess the presence and severity of sleep problems, while one of them (AIS) addresses also the diagnosis of insomnia. Other instruments, e.g. , Structured Clinical Interview for DSM-IV (SCID) [48], Epworth Sleeping Scale (ESS) [49], provide insights into insomnia consequences and co-morbidity with other sleep disorders or other psychiatric conditions. These methods, together with sleep laboratory studies, have provided useful findings and have significantly increased our knowledge about insomnia. However, longitudinal studies are needed to further our understanding of the pathophysiology and the morbidity of insomnia, defining roles for risk factors, hyperarousal and co-morbidities, as well as the effect of treatment in long-term disease progression [35].

Treatment of insomnia

The effective management of insomnia begins with recognition and adequate assessment. Family doctors and other health care providers should routinely enquire about sleep habits as a component of overall health assessment. Identification and treatment of primary psychiatric disorders, medical conditions, circadian disorders, or specific physiological sleep disorders, such as sleep apnea and periodic limb movement disorder, are essential steps in the management of insomnia [8].

Insomnia may be distinguished in two different states. The first is a state of transient insomnia due to an acute event, while the second is the state of chronic insomnia. What is required in the first case is a treatment lasting for a few days only, i.e. , for the period of the underlying event that caused insomnia. Such a case requires a medicine able to induce sleep immediately, while its effect quickly diminishes, so that the individual does not experience after effects when awakened. In the case of chronic insomnia, i.e. , when a person cannot relax in order to fall asleep, the therapeutic effort should be aimed at the reduction of chronic stress. The objective is to reduce the level of arousal when going to bed. Thus, the treatment may be more on a psychological basis, employing psychotherapeutic techniques, so that the patient can control the levels of his or her stress. In fact, all psychotherapeutic techniques, ranging from those of a psychoanalytical nature to those of behavioral or cognitive orientation, aim at a long-term reduction of the patient's inner conflicts and levels of stress. Consequently, all successful psychotherapeutic endeavors lead to a more effective stress management, creating relaxation and smooth sleep induction. Another important factor, however, in the management of insomnia is that patients should be informed about the underlying mechanisms causing their disorder. Therefore, a clarification of the physiological function of sleep, as well as the decline in the need for sleep as the individual grows older, helps at reducing stress linked to sleep disturbances. It is common that old people want to sleep more hours than are needed.

However, it is known that even older adults who do not complain of insomnia, manifest significantly disturbed sleep relative the younger subjects, indicating that many healthy older individuals apparently adapt their perception of what is "acceptable" sleep for their age [50].

It is worth mentioning that patients with primary insomnia overestimate their sleep onset latency and underestimate their total sleep time. In a recent study, when individuals with primary insomnia realized how distorted their perception of sleep was, they reported less anxiety and preoccupation about sleep [51]. In this context cognitive behavior therapy may be useful in young and middle-age patients with sleep-onset insomnia [52]. On the other hand, an effective sleep-inducing medication generates a feeling of reassurance to an insomniac patient. Knowing that, in case they cannot sleep, there is an effective drug at their disposal helps insomniacs reduce their stress and facilitates both the sleep induction and the overall quality of their sleep.

It is, therefore, inferred that apart from the psychologically oriented means of treating chronic insomnia, drugs can also be helpful. It should be mentioned, however, that drugs could help in two different ways. On the one hand, they may generate reassurance, as mentioned above. On the other hand, they may be used for generally reducing the level of stress. However, while in the first case the appropriate drug is a hypnotic of rapid effect and short half-life, in the second case the doctor should rather resort to a minor tranquilizer of longer half-life. In any event, approved hypnotic drugs have clearly been shown to improve subjective and objective sleep measures in various short-term situations [53].

Despite widespread use of standard hypnotics and sedating antidepressants for chronic insomnia, their role for this indication still needs to be defined by further research [8]. In particular, clinicians must be cautious with antidepressants, which disturb sleep architecture and have various side effects [54, 55].

On the other hand, hypnotics, although they improve total sleep time as well as sleep onset latency during short-term use, induce rebound insomnia after cessation of treatment [56, 57]. This is pertinent not only for the short half-life benzodiazepines, but also for newer hypnotic drugs such as zolpidem [58], whereas when they were first launched, there were reports of a more favorable profile for rebound insomnia and daytime anxiety [59]. Moreover, a recent review of controlled trials that compared benzodiazepines to the Z-drugs (zaleplon, zolpidem and zopiclone), for short-term management of insomnia, concludes that short-term-acting drugs are equally effective [60].

In clinical practice, it is not rare to find chronic insomniacs taking a hypnotic for years. In this population, a progressive 15-day withdrawal, may not help avoiding an immediate worsening of sleep parameters [61]. Furthermore, discontinuation of the hypnotic has been demonstrated to be a very difficult task for prolonged users of benzodiazepines, even when their medication taper was combined with cognitive-behavior therapy [62].

However, to avoid rebound insomnia as well as the progressive diminishing of effectiveness of the hypnotics during the chronic use, it has been suggested that they are not taken every night. This intermittent dosing strategy, which has recently been gaining popularity among clinicians, has been documented to be effective [63].

The hormone melatonin is involved in the control of the circadian system, and has been implicated in the control of sleep [64]. Several studies have examined the effectiveness of melatonin as a treatment of insomnia. While some researchers have reported a positive effect [65, 66], others have reported little or no effect [67, 68]. At present, the magnitude of beneficial effects following melatonin administration to insomniacs is unclear. Furthermore, the mechanism of action of this hormone with relation to sleep initiation, has not yet been fully described [69]. Finally, exposure to bright light therapy during the early morning hours has been reported to relieve sleep onset insomnia, even in elderly patients [70]. This may be due to the restoration of circadian rhythms in these insomniacs.

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Neuropharmacology of obstructive sleep apnea and central apnea

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Introduction

Obstructive sleep apnea (OSA) and other forms of sleep-disordered breathing including central sleep apnea (CSA) are amongst the most common sleep disorders. The prevalence of the most severe form of OSA, the OSA syndrome (OSAS; OSA plus co-existing sleepiness), ranges between 3–7.5 % in males and 2–3 % in females [1]. Lesser degrees of OSA may well affect up to 28 % of the adult population [2]. Simple snoring shares pathophysiological features with OSA, and affects even greater numbers. CSA is seen mainly in patients with cardiac failure and less commonly in stroke or other neurological conditions. While there are a range of more or less effective non-pharmacological therapies for both OSA and snoring, and for CSA, all such therapies are problematic and there is a clear and pressing need for efficacious and safe pharmacological treatment for these sleep disorders.

Obstructive sleep apnea

OSA definition

Factors that predispose to OSA include obesity, gender, age, ethnic (including genetic) factors, and craniofacial structure, and OSA may be aggravated by use of certain drugs and smoking. It is pathophysiologically characterized by repetitive episodes during sleep of upper airway narrowing and/or closure, accompanied by increased breathing efforts in attempts to overcome such narrowing/closure, also by arousals and/or outright wakenings from sleep, as well as attendant respiratory and cardiovascular perturbations such as hypoxia, systemic and pulmonary hypertension and tachy- and bradycardia. The adverse effects of OSAS are well documented, and include poor sleep quality and consequent neurobehavioral dysfunction, reduced daytime vigilance and excessive daytime sleepiness, and risk for motor vehicle and other accidents, and cardiovascular morbidity and mortality [3–8]. A full description of the epidemiology, the diagnosis and clinical correlates of OSA has been presented recently [1, 2, 9–12].

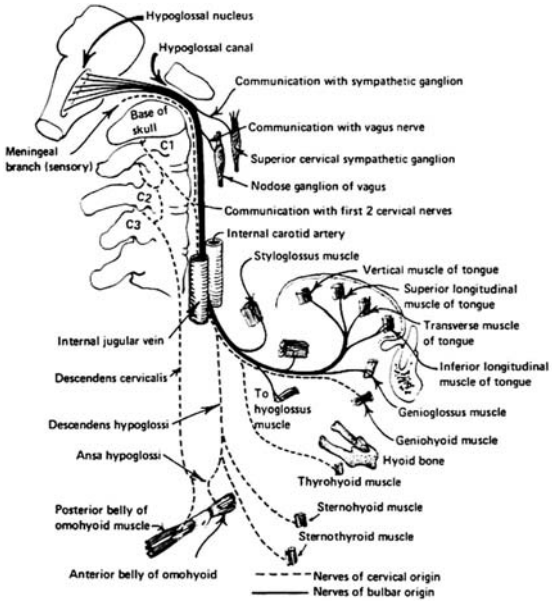

Fig. 1. Innervation of relevant upper airway musculature. From [13] with permission from Elsevier

Non-pharmacological therapies for OSA

The most effective non-pharmacological therapy currently available is (nasal) continuous positive airway pressure (nCPAP), but even so this therapy may be unacceptable or be used irregularly in over 50 % of patients prescribed nCPAP [14]. Tracheostomy is an effective surgical treatment for OSA but not currently recommended except in the most extreme circumstances. Other surgical procedures have included uvulopalatopharyngoplasty but substantial evidence for benefit is lacking [15]. Facial reconstructive surgery has a limited role in individuals with OSA secondary to facial dysmorphia. Oral appliances including mandibular advancement splints (MAS) may have a role in treating mild or moderate degrees of OSA, but long-term compliance is uncertain, and occasionally dental malocclusion and tempero-mandibular joint dysfunction may eventuate with use of MAS [16, 17]. These non-pharmacological therapies of OSA share a number of features, such as variable efficacy, significant side-effect profile, potentially high cost and reliance on skilled technical intervention, and lack of patient acceptance, which in concert argue strongly for the promotion of effective pharmacological therapies for OSA.

Neuropharmacology of the upper airway

Individuals with OSA usually have structural narrowing of the upper airway but are able to maintain upper airway patency in wakefulness, albeit with increased levels of genioglossus muscle (the major pharyngeal dilator) activity compared to

controls [18]. Upper airway obstruction in sleep is ultimately caused by processes that affect the motor control of the pharyngeal muscle dilators (Fig. 1), and that control is mediated through the actions of relevant neurotransmitters impacting on motor neurons particularly of the hypoglossal nerve. Thus, an important prelude to consideration of specific pharmacological therapies in OSA is to outline current understanding of the neuropharmacology of the upper airway.

There are many neurotransmitters present in the motor nuclei of upper airway dilator motor neurons in the brainstem, and more centrally in the central nervous system (CNS), which are implicated in the neural control of upper airway patency [19, 20]. Glycine and γ-aminobutyric acid contribute inhibitory influences on upper airway motor neuronal activity [21]. Other neurotransmitters such as acetylcholine, glutamate, noradrenaline, thyrotropin-releasing hormone, substance P, vasopressin, oxytocin and orexin also have roles, but the pre-eminent excitatory neurotransmitter is serotonin (5-hydroxytryptamine, 5-HT) [22]. The relative importance and interplay between these neurotransmitters has been studied *in vitro* in reduced motor neuron preparations, and *in vivo* in healthy animals including cats, rats and a natural animal model of sleep-disordered breathing, the English bulldog. It is likely that there will be some differences between the results of these studies and the interplay of brainstem upper airway motor neuron neurotransmitters in human adults with established sleep-disordered breathing.

Serotonin

Support for serotonin having a prominent role in the neurochemical basis of upper airway patency is provided by excitation of brainstem dilator motor neurons by local administration of serotonin [23–26], and conversely by reduction of brainstem motor neuron activity by local administration of serotonin antagonists [25, 27, 28]. Identified serotonergic brainstem motor neurons increase activity linearly with respiratory motor challenges [29], and nucleus raphe pallidus serotonin-containing motor neurons that innervate brainstem motor neurons implicated in upper airway dilator muscle activity become less active in non-rapid eye movement (NREM) sleep and virtually absent in REM sleep [30–32]. Microperfusion of serotonin into brainstem hypoglossal motor nuclei protects against sleep-related suppression of upper airway dilator muscle activity in NREM sleep, and attenuates the suppression seen in REM sleep [33]. Systemic administration of serotonin antagonists in the English bulldog produces obstructive breathing in wakefulness [34], attesting to the importance of this neurotransmitter to the maintenance of airway patency in the wake state in this model. Importantly, the administration of serotonergic drugs (L-tryptophan and trazadone) in the English bulldog produces a dose-dependent reduction in measures of sleep-disordered breathing, more markedly in NREM sleep [35].

Serotonin receptors

The neurochemical control of upper airway motor neurons is complex, and that complexity is significantly contributed to by the existence of at least 18 serotonin

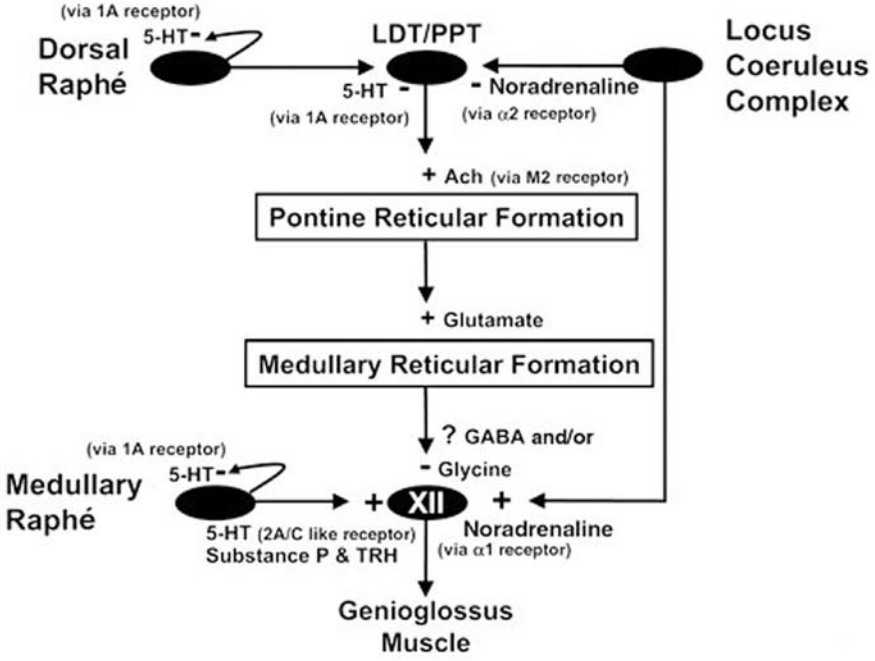

Fig. 2. Schema of the neuronal circuitry that is currently believed to be involved in the pontine regulation of rapid eye movement (REM) sleep progressively disinhibits pontine cholinergic neurons preceding and during REM sleep progressively disinhibits pontine cholinergic neutones of the laterodorsal and pedunclopontine tegmental nuclei (LDT/PPT) via withdrawal of serotonin (5-HT)-mediated and noradrenaline-mediated inhibitory inputs. Activation of these LDT/PPT neurones then leads to increased acetylcholine (ACh) release into the pontine reticular formation, resulting in activation of the neuronal systems that mediate ascending and descending signs of REM sleep (e.g. cortical desynchronization end motor atonia, respectively). Exogenous application of a cholinergic agonist (e.g. carbachol) by microinjection into the pontine reticular formation is used to mimic this process end trigger REM-like neural events in reduced preparations (e.g. anaesthetized or decerebrate animals). Postural motor atonia in REM sleep is produced by postsynaptic inhibition of motor neurones by γ-aminobutyric acid (GABA) and glycine. Neurones of the medullary reticular formation are thought to drive this inhibition, themselves being driven by neurones in the pontine reticular formation (the reticular structures are indicated by the boxes). Whether hypoglossal (XII) motor neurones are also postsynaptically inhibited in REM sleep by similar mechanisms is uncertain. Hypoglossal motor neurones also receive excitarory inputs from the locus coeruleus complex and medullary raphe that many also contribute to reduced genioglossus muscle activity in sleep, especially REM sleep. Corelease of thyrotropin-releasing hormone (TRH) and substance P from raphe neurones may contribute to this process. The influences of other neural systems that are potentially modulated by sleep states are not included for clarity. See text (of original article) for more details. $+$, excitation; $-$, inhibition; M, muscarinie. Reproduced from Fig. 2 of [36]

receptor subtypes [37]. Such diversity of receptor subtypes is played out across both the CNS and peripheral nervous system (PNS). The predominant receptor subtype in hypoglossal motor neurons is 5-HT_{2A}, but 5-HT_{2C} is also present, and both postsynaptic subtypes being excitatory [38]. Other receptor subtypes are present in smaller quantities when measured by a semi-quantitative technique, and receptor subtypes such as 5-HT_4, 5-HT_6 and 5-HT_7 may also have an excitatory role in upper airway motor neurons [38] (Fig. 2). Stimulation of a presynaptic receptor, 5-HT_{1B}, is inhibitory to hypoglossal neuron activity [39], thereby providing a local negative feedback loop. Furthermore, although not present directly on hypoglossal motor neurons, stimulation of 5-HT_3 receptors on interneurons connecting with hypoglossal neurons likely has inhibitory effects on hypoglossal motor output [40]. There are excitatory serotonergic effects on respiratory neurons at other points in the brainstem CNS involving the 5-HT_2 and 5-HT_{1A} receptor subtypes [41, 42].

In the PNS, specifically at the nodose (inferior vagal) ganglion, stimulation of 5-HT_2 and 5-HT_3 receptor subtypes suppresses respiration [43]. Administration of the 5-HT_3 antagonist ondansetron reduces CSA in rats through this peripheral effect [44, 45], and reduces sleep-disordered breathing in REM sleep in the English bulldog, without influencing changes in NREM sleep [46] (see section 'Ondansetron' below for its effects in humans).

There is some evidence that long-term intermittent hypoxia analogous to the hypoxic exposure of human cases of OSAS, may predispose to oxidative injury to upper airway brainstem neurons, i.e. , hypoglossal motor neurons, and thereby diminish potential serotonergic excitatory responsiveness. At least in Sprague-Dawley rats exposed to 3 weeks of intermittent hypoxia, unilateral serotonin and glutamate agonist and antagonist microinjections, respectively, into the hypoglossal motor nuclei showed reduced hypoglossal nerve responsiveness (log EC_{50}) for serotonin and N-methyl-D-aspartate (NMDA) [47]. These results may explain at least in part the modest or absent responses to serotonergic drug therapy in OSA patients (see below).

Serotonergic drugs

L-Tryptophan

Serendipity led to an early trial of L-tryptophan in 15 patients with sleep-disordered breathing, but the study used non-uniform dosage schedules, was unblinded and non-placebo controlled. Nevertheless, there were encouraging reductions in markers of sleep respiratory disturbance particularly in NREM sleep [48]. Subsequent reports of eosinophilic myalgic syndrome and life-threatening pulmonary hypertension with use of L-tryptophan [49] led to withdrawal of this drug preparation, and stymied interest in this general class of drug therapy for several years.

Buspirone

Buspirone is a partial 5-HT_{1A} agonist, and systemically is a respiratory stimulant; it has been used as an anxiolytic. In a small trial of five OSAS patients there was an overall modest reduction of the apnea index (though worsening in one of these patients) [50].

Specific 5-HT$_{2A/2C}$ receptor agonists
The 5-HT$_{2A/2C}$ receptor agonist [±]-2,5-dimethoxy-4-iodoaminophentamine improved upper airway collapsibility in Zucker rats, but had complex other effects, including increasing upstream airways resistance, while maintaining unchanged maximal airflow [51]. Studies in humans are not available at this time.

Fluoxetine
Fluoxetine is a selective serotonin-reuptake inhibitor (SSRI) that produces a net increase in (post-synaptic motor neuron) serotonin delivery after 4–6 weeks of use. A double-blind, randomized cross-over trial compared fluoxetine to the tricyclic antidepressant agent protriptyline and placebo in 12 patients with sleep-disordered breathing [52]. The group apnea-hypopnea index (AHI) improved with fluoxetine compared to placebo, but there was great variability of response and other measures of disordered sleep did not change. These potentially beneficial results in a small number of patients need to be replicated in well-designed larger studies to support a useful role in clinical practice.

Paroxetine and trazodone
Paroxetine is another SSRI that has undergone a trial in a small number of patients with mild to moderate sleep-disordered breathing, and been shown to produce modest decrements of the apnea index in NREM sleep only [53]. Trazodone is a weak SSRI, and its metabolite is a powerful 5-HT$_{2C}$ agonist that can cross the blood-brain barrier. Its beneficial effects (in combination with L-tryptophan) on sleep-disordered breathing have been noted in the English bulldog [35], and also documented in a case report of a patient with olivopontocerebellar degeneration manifesting both obstructive and CSA events [54].

Mirtazapine
Mirtazapine is an antidepressant that increases both serotonin and noradrenaline by blockade of central α_2 auto- and heteroreceptors; mirtazapine also blocks 5-HT$_2$ and 5-HT$_3$ serotonin receptor subtypes, and that former property may induce slow-wave sleep. Systemic administration of mirtazapine has been shown to increase genioglossus muscle activity in anesthetized rats in a dose-dependent manner [55]. In a randomized, double-blind, cross-over trial of ten patients with OSA, mirtazapine at a dose of 15 mg reduced the AHI by 50 %, and the arousal index by some 29 % [56]. Side-effects with use of mirtazapine include somnolence and hyperphagia/weight gain.

Ondansetron
As mentioned above, the 5-HT$_3$ antagonist ondansetron has a salutary effect on CSA in rats and on REM-related sleep-disordered breathing in the English bulldog model of OSA. However, in the only human trial of this drug in ten patients with moderate OSA, compared to placebo, there was no effect on sleep architecture nor on any index of sleep-disordered breathing [57], although the postulated tissue levels of active drug in this trial were an order of magnitude below that in the English bulldog study.

Cannabinoids
Interest has accrued in recent years in the endogenous cannabinoid neuromodulatory system, whose effects are mediated by two recognized receptors, CB_1 and CB_2. Both exogenous and endogenous cannabinoid ligands may impact sleep/wake and autonomic behaviors, in part at least through interactions with serotonin receptor function. Exogenous Δ^9-tetrahydrocannabinol and the endogenous cannabinoid ligand oleamide both stabilized respiration in all sleep stages in instrumented Sprague-Dawley rats, significantly reducing the apnea index in both NREM and REM stage sleep [58]; both agents blocked serotonin-induced exacerbation of apnea consistent with a coupling between cannabinoids and specific serotonin receptors ($5\text{-}HT_3$) in the PNS. The potential exists for human trials of exogenous cannabinoids in the pharmacological treatment of OSA, but such trials are lacking to date. Interestingly, the CB_1 selective blocker rimonabant is currently undergoing trial as a weight-loss and smoking-cessation agent [59], and therefore may have potential use in OSA patients with co-existing obesity.

Pro-inflammatory cytokines and anti-cytokine therapy

There is emerging evidence that OSA may be a pro-inflammatory disorder with elevated circulating cytokines [60]. Abdominal visceral fat is a major reservoir of cytokines, and obesity is a leading risk factor for the presence of OSA [60]. The mechanism(s) whereby pro-inflammatory cytokines are elevated in OSA is not fully elucidated, but may be related to the excessive sympathetic nervous system activation notable in OSA. Tumor necrosis factor (TNF)-α and interleukin (IL)-6 levels are elevated in OSA [61, 62] and the circadian rhythm of TNF-α is disrupted in OSA [63]. IL-6 levels are higher again in OSA patients with systemic hypertension compared to normotensive apneics [60]. IL-6 levels return to normal in OSA patients treated effectively with CPAP [64]. Other mediators of inflammation elevated in OSA include intercellular adhesion molecule-1 and C-reactive protein, the latter being synthesized primarily in hepatocytes in response to IL-6 [60]. The presence of these and other pro-inflammatory cytokines may link to the increased prevalence of cardiovascular morbidity in OSA.

Anti-cytokine therapies using anti-TNF-α and anti-IL-6 monoclonal antibodies are finding roles in the treatment of other medical conditions, such as rheumatoid arthritis, but are yet to be widely studied in the treatment of OSA, and may perhaps best be considered as adjunctive therapy in patients incompletely treated with other modalities such as CPAP. In a small placebo-controlled study the anti-TNF-α agent etanercept improved sleepiness in OSA patients, reduced levels of the cytokine IL-6, and had a very modest benefit on the AHI [65]. Increased direct vagal nerve stimulation significantly attenuates release of TNF-α in an animal model of the systemic inflammatory response to endotoxin [66], and OSA patients have been shown to have attenuated vagal activity [67]. Perhaps drugs enhancing this vagal efferent activity may have a therapeutic role in OSA in the future.

Other drug therapies

Tricyclic antidepressants

There may be some amelioration of sleep-disordered breathing in OSA patients treated with tricyclic antidepressants, such as protriptyline and imipramine, possibly through a REM stage-restricting effect [68, 69]. Improvement in the OSA symptom of daytime sleepiness, independent of any effect on sleep quality or architecture, has been reported in some studies with protriptyline [70]. However, a recent Cochrane Systematic Review comparing studies using protriptyline and placebo found no significant advantage for the active drug in terms of AHI or any other objective measure of respiratory disturbance in sleep [70].

Sex steroids

There are compelling epidemiological reasons to consider the possibility that hormone replacement therapy in postmenopausal women with OSA, and use of anti-androgens in males with OSA, may be of therapeutic benefit. However, the results of such interventions in therapeutic trials have been disappointing [71]. However, the administration of medroxyprogesterone (MPG) to patients with the most severe form of OSAS, the obesity hypoventilation syndrome in which daytime hypercapnia and nocturnal/sleep hypoventilation are integral clinical features, produces a beneficial ventilatory stimulant effect [71]. In contrast, a single placebo-controlled study of ten male patients with OSA treated with MPG did not demonstrate any difference in measured outcomes of AHI or total sleep time [72]. Furthermore, the significant range of adverse effects of this agent severely limit its applicability.

There are no studies that show convincingly that hormone replacement therapy reduces sleep apnea severity in postmenopausal women with OSA [73–76].

Anti-hypertensive agents

Chronic systemic hypertension is certainly a common association of OSA. Acute blood pressure rises also occur during termination of apneas. Short-term trials of anti-hypertensives in OSA have had varying modest effects on indices of sleep-disordered breathing. Cilazapril, an ACE inhibitor, and the β-blocker metoprolol both reduce AHI by about 30 % in OSA patients [77]. Some calcium antagonists (isradepine, mibefradil) have also been shown to have similar modest beneficial effect in small numbers of OSA patients [78, 79]. The α adrenergic agonist clonidine reduced OSA features in REM sleep in six of eight patients, but not in NREM, and overall there was no significant difference in AHI or overnight minimal oxygen saturation [80]. On a cautionary note, in a few patients in these trials of anti-hypertensives there was actually worsening of OSA features [78, 80].

Physostigmine

The cholinesterase inhibitor physostigmine has been investigated in a small blinded, placebo-controlled study of moderate to severe OSA patients, and via steady-state intravenous infusion been shown to modestly decrease the overall AHI and severity of oxygen desaturation, predominantly in REM compared with NREM sleep [81]. The exact mechanism of the beneficial action of physostigmine in sleep apnea is not clear.

Novel therapy

A novel approach to the treatment of OSA has used the intrapharyngeal application of an exogenous surfactant preparation, which lowers the surface tension of upper airway lining liquid and thereby reduces upper airway opening and closing pressures. In a small group of severe OSA patients the measured fall in surface tension was correlated with a significant though small reduction of respiratory disturbance index [82].

Pharmacological treatments of OSA risk factors and morbidities

Rather than considering OSA as an isolated condition for treatment, it is also important to consider risk/aggravating factors such as obesity, alcohol consumption, cigarette smoking and obstructive nasal pathologies. Furthermore, some of the important resultant morbidities of OSA such as hypertension (discussed above) and neurobehavioral dysfunction, particularly manifesting as excessive daytime sleepiness, also warrant early and direct therapeutic approaches. The roles of anti-obesity drugs, alertness-promoting drugs and other drugs are therefore discussed below.

Anti-obesity drugs

Obesity predisposes to OSA, progressive weight gain worsens established OSA and weight loss ameliorates the severity of OSA [2, 83–86]. Reducing weight may achieve benefit in OSA through improvement to upper airway caliber (by reducing fat deposition in the lateral pharyngeal wall and tongue), by improvement of residual lung volume (and thus of overall lung function) and by reducing whole body oxygen demand [2, 87, 88]. Generally, anti-obesity drugs are not first-line therapy in the treatment of obesity and are usually recommended as supplementary to a dietary and exercise program where such options are practicable. Some therapies such as of the general class of noradrenergic drugs are FDA recommended only for short-term use. Other weight-loss agents such as ephedrine/ephedra combined with caffeine, though effective, have significant safety concerns and are not recommended. A comprehensive overview of the management of obesity, including drug therapy, is beyond the scope of this chapter and the interested reader is referred elsewhere [89–91]. A brief summary only of the major anti-obesity drug options is given here.

Psychotropic anti-obesity drugs

That particular psychotropic drugs such as the SSRI antidepressants fluoxetine (see also above), sertraline and fluvoxamine may be useful as weight-loss agents was initially suggested by the unexpected observation of weight loss in trials of these agents in patients treated for neuropsychiatric conditions [92]. Subsequently, randomized controlled trials were specifically designed to assess their efficacy as weight-loss agents in obese patients without neuropsychiatric co-morbidities. Of these agents, fluoxetine has been the most studied, in obese subjects without attendant co-morbidities [93], in obese subjects with diabetes [94, 95] and in obese subjects with eating disorders [96]. Short-term (8 weeks) studies in the first group showed an approximate weight loss of about 4 kg compared with placebo, though doubts have surfaced about sustained benefit in longer-term studies. Trials of fluoxetine as a weight-loss agent in obese type 2 diabetics have shown mixed results. Fluoxetine has shown to be efficacious and well tolerated in obese patients with binge eating disorder and bulimia nervosa.

Bupropion increases noradrenaline turnover and blocks reuptake of dopamine but does not affect serotonin reuptake. It is used as an antidepressant and to aid smoking cessation. In depressed patients bupropion was noted to engender significant weight loss, and limited weight gain in smoking cessation trials [97, 98]. In studies specifically designed to assess the anti-obesity properties of bupropion in subjects without neuropsychiatric co-morbidities, weight losses of 7.5–13 % of initial weight was achieved after 8–12 months treatment, and was generally well tolerated [99, 100].

There has been limited short-term experience as anti-obesity agents with the SSRI citalopram [101, 102], and with the serotonin-noradrenaline reuptake inhibitor venlafaxine [103], and no recommendations can be made re use of these agents solely as anti-obesity therapy in clinical practice.

Topiramate can be described as a broad-spectrum neurotherapeutic agent with multiple modes of action, and its weight-loss promoting activity came to attention in trials of therapy for epilepsy [104], and explored further in animal experiments [105, 106]. It has also been successfully used in the treatment of obesity associated with eating disorders [107, 108]. As specific weight-loss therapy in one short-term [109] and one long-term study [110] in non-diabetics without co-morbid neuropsychiatric conditions, topiramate has been shown to produce a modest dose-related benefit compared to placebo, and with a reasonable side-effect profile.

Zonisamide is an anti-epileptic with serotonergic, dopaminergic and other properties, and also has been associated with weight loss in clinical trials of treatment of seizure disorders [111]. In a single trial to adjudge efficacy as a weight-loss agent in obese individuals without co-morbid neuropsychiatric conditions, zonisamide was well tolerated and associated with a weight loss of 9.2 kg at 32 weeks [112].

Other anti-obesity drugs

Sibutramine is a specific inhibitor of noradrenaline and serotonin reuptake into nerve terminals, and is believed to inhibit food intake by promoting satiety [113]; it may also increase thermogenesis [114–116]. Short- and long-term clinical trials of sibutramine in obese subjects documents weight loss of approximately 10 % of initial weight with

continued use [117–119]. The main potential adverse effects are increased blood pressure and heart rate, and the drug is contraindicated in cardiac conditions, and in patients who have had stroke, or are using monoamine oxidase inhibitors or SSRIs. In patients with obesity and OSA, sibutramine has a similar weight-loss profile and predictable associated improvements in indices of sleep-disordered breathing [86]. Sibutramine is FDA approved for long-term use to aid/maintain weight loss.

Orlistat alters fat metabolism by inhibiting pancreatic lipases with consequent increased fecal fat excretion. Long-term trials confirm orlistat's ability to promote approximately 10 % weight loss [120, 121], and to help prevent weight regain [122]. Main side effects are discomforting gastrointestinal symptoms such as excessive borborygmi, cramps, flatus, etc. Orlistat also may produce an improvement in lipid profile unexplained by the degree of weight loss [123]. It is FDA approved for long-term use.

A number of peptides including leptin, glucagon-like peptide-I and peptide YY induce weight loss in experimental animals and in humans [124, 125] but are not currently approved for use by the FDA or other regulatory bodies in the clinical treatment of obesity.

Alertness-promoting drugs

Alertness-promoting drugs have a well-recognized primary role in the treatment of conditions in which excessive daytime sleepiness (EDS) is a prominent or the major symptom causing disablement, conditions such as narcolepsy and idiopathic hypersomnolence. The use of such medications in other disorders where EDS persists despite treatment of the underlying pathophysiology with directed treatments (e.g. , nCPAP in OSA) is controversial. Alertness-promoting drugs (also known as stimulants) can be classified as sympathomimetic (examples include the amphetamines, methylphenidate, pemoline) or non-sympathomimetic (modafinil, caffeine).

Modafinil

The action of modafinil, though presently not fully understood, is thought to be mediated largely by dopamine [126]; it is possible that it may also affect the histaminergic system [127] and inhibit release of GABA in the hypothalamus [128], influence serotonin release and, at least in rats, reduce noradrenaline reuptake [129]. In the case of persisting EDS in CPAP-treated OSA patients, modafinil has been shown to improve Epworth Sleepiness Scale (ESS) scores and multiple sleep latency test (MSLT) results compared to placebo in a short-term trial of therapy [130]. Other short-term studies have documented improvements in sleep-related functional health status and ESS scores [131], or improved the frequency of lapses of attention during psychomotor vigilance performance testing [132]. On the other hand, another study of modafinil in this context did not show improvements in MSLT latency or ESS score, but did show a marginal improvement in the latency of the maintenance of wakefulness test (MWT) [133]. A recent longer (12 week) study has also confirmed the useful role of modafinil in these circumstances, documenting improvements in MWT latencies, ESS score and overall clinical condition [134].

Other drugs

Sabeluzole and NMDA receptor antagonist AR-R15896AR
Glutamate may be the neuromediator responsible for ventilatory stimulation during acute hypoxia, and thereby may contribute to the ventilatory instability present during sleep in OSA. It was postulated that it may be possible to decrease ventilatory variability in OSA by the use of the glutamate antagonist sabeluzole. In a small study of sabeluzole in OSA patients, compared to placebo there was no overall improvement in oxygenation, although higher levels of the drug were associated with improved sleep levels of oxygen in some individual patients [135]. In a study examining hypoxemia-induced glutamate release into the CNS, the potential benefit of antagonism of glutamate effects mediated by postjunctional NMDA receptors was examined in a placebo-controlled double-blind study in 15 patients with OSA. However, the NMDA receptor antagonist AR-R15896AR did not significantly affect AHI or oxygen saturation variables in this context [136].

Central sleep apnea

CSA is defined by an absence of at least 10 s duration of both airflow and respiratory effort in sleep, and central hypopnea indicates a reduction of these parameters causing reduced tidal volume. CSA comprises a heterogeneous group of congenital and acquired disorders, and in the latter grouping neurological conditions affecting the brainstem include the stroke syndromes of cerebrovascular disease. CSA is also seen in a striking proportion of males with left ventricular cardiac failure (33–40 %) [137, 138], and OSA may coexist in some of these patients [139]. CSA is also seen in high-altitude exposure and uncommonly in miscellaneous other medical conditions.

Pathophysiology and clinical context of CSA

In the CSA of cardiac failure, recumbent pulmonary venous congestion stimulates vagal pulmonary afferents causing hyperventilation and hypocarbia, and arousals further stimulate ventilation and drive hypocarbia below the apnea threshold. The apneas and hypoxia of CSA promote sympathetic nervous system activation and negative cardiovascular consequences for the cardiac patient. There is currently no consensus for the optimal treatment of CSA in cardiac failure [139]. Optimizing cardiac failure drug therapy with diuretics, ACE inhibitors and β-blockers and other specific cardiac medications should be pursued. Supplementary nocturnal oxygen therapy has been shown to have salutary effects in short-term trials of therapy of CSA in cardiac failure [140, 141]. Various forms of noninvasive positive airway pressure support during sleep have been tried in CSA of cardiac failure but to date only CPAP has been shown to have beneficial short-term functional and symptomatic effects [142–144] and, in a small study, long-term improvement in mortality or progression to cardiac transplantation [145]. However, results of the larger ($n = 258$) CANPAP study of CPAP use in heart failure patients with CSA, showed no difference in primary

endpoints (mortality or heart transplantation) between the nocturnal CPAP-treated group and the non-CPAP group after a mean follow-up of 2 years [146].

Acetazolamide

Acetazolamide is a carbonic anhydrase inhibitor that produces a metabolic acidosis, thereby stimulating ventilation, and a consequent shift in the arterial carbon dioxide tension that defines the apnea threshold. It has been used successfully to treat the CSA of high altitude, but there is not an extensive literature on its more general use in CSA. Side effects including paresthesia are common and may preclude continuation of therapy. Interestingly, acetazolamide has also undergone trials in OSA patients with objective benefit, but again tolerability of the drug was a problem [147].

Theophylline

Although theophylline has been shown to reduce CSA events in a small number of compensated cardiac failure patients [148], the drugs arrhythmogenic potential in advanced cardiac failure patients probably precludes its long-term use.

Summary and future directions

There has been limited progress in the development of effective pharmacotherapy for sleep apnea. A range of agents has been utilized, but there has been lack of or only modest benefit in the treatment of OSA and CSA using these agents. A number of drug therapies are limited as well by significant side effects. The promise of serotonergic drug therapy is yet to be realized, and further developments await the full exploration and understanding of the complex interplay of the various and often counteractive 5-HT receptor subtypes in the CNS and PNS that in concert may affect upper airway patency in sleep and wake states. It is possible that effective OSA drug treatment may necessitate combination drug therapies, for example so that excitatory stimulation of upper airway dilator muscles in sleep is combined with pharmacological inhibitory actions on constrictor/relaxant mechanisms.

Given the lack of acceptance of CPAP in mild to moderate cases of OSA, better understanding of the neuropharmacology of OSA and potential pharmacotherapies is imperative.

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Narcolepsy syndrome: a new view at the beginning of the second millennium

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Introduction and history

The term 'narcolepsy' was first coined by Gélineau [1] in 1880 to designate a pathological condition characterized by irresistible episodes of sleep of short duration recurring at close intervals. Although Westphal [2] and Fisher [3] had previously published reports of patients with sleepiness and episodic muscle weakness, Gélineau was the first to characterize narcolepsy as a distinct syndrome. He wrote that attacks were sometimes accompanied by falls, or "astasias". Henneberg [4] later referred to these attacks as 'cataplexy'. In the 1930s, Daniels [5] emphasized the association of daytime sleepiness, cataplexy, sleep paralysis, and hypnagogic hallucinations. Referring to these symptoms as 'the clinical tetrad', Yoss and Daly [6] and Vogel [7] reported nocturnal sleep-onset rapid eye movement (REM) periods in narcoleptic patients, a finding confirmed in the following years [8–11]. Participants in the First International Symposium on Narcolepsy, held in France in 1975, defined the syndrome as follows:

The word 'narcolepsy' refers to a syndrome of unknown origin that is characterized by abnormal sleep tendencies, including excessive daytime sleepiness and often disturbed nocturnal sleep and pathological manifestations of REM sleep. The REM sleep abnormalities include sleep onset REM periods and the dissociated REM sleep inhibitory processes, cataplexy and sleep paralysis. Excessive daytime sleepiness, cataplexy, and less often sleep paralysis and hypnagogic hallucinations are the major symptoms of the disease [12].

Prevalence, genetics, and environmental factors

In the United States and the United Kingdom, the estimated prevalence of narcolepsy is 1 per 2000 (0.05 %) [13, 14]. The prevalence of narcolepsy ranges from 0.16–0.18 % in Japan to 0.002 % in Israel [15]. There is no gender difference, and age of

onset is usually between 13 and 24 years. In approximately 6 % of patients, symptoms start before the age of 10 [16]. Although most cases occur sporadically, some occur in familial clusters. The risk for a first-degree relative of a narcoleptic developing narcolepsy is 10–40 times higher that in the general population [15].

After the report by Fuji et al. in 1984 [17] in Japan of a tight association between narcolepsy and HLA DR2, many studies have been performed on patients with excessive daytime sleepiness (EDS) and with or without cataplexy. Typing evolved from serological to high-resolution determination. It was found that ethnicity and related presence or absence of linkage disequilibrium between specific alleles had an impact on the major susceptibility allele for the presence of narcolepsy with cataplexy. In the Japanese and a high percentage of Caucasians DQ B1-0602 is very tightly associated with DR B1-1502 [18, 19], while in African Americans and in Martinicans, with variable mixtures of African and Caucasian origins [20–22], an absence of linkage disequilibrium was demonstrated. This absence of linkage disequilibrium in that group indicated that DQ B1-0602 was the major HLA susceptibility allele for EDS with cataplexy across ethnic groups [22]. Depending on the series, and independent of ethnicity, 88-98 % of patients with clear cataplexy are HLA DQ B1-0602. Further studies on Caucasians with cataplexy and EDS have shown that, when considering susceptibility for cataplexy and EDS, both DQ A1-0102 and DQ B1-0602 are present, suggesting complementation [23], and indicating that these two alleles may be important for disease predisposition. HLA DQ B1-0602 homozygotes have a two to four times higher risk of developing cataplexy with EDS than heterozygotes [24]. Investigations of heterozygosity and different alleles of DQ B1 have shown that some are protective, while others favor narcolepsy-cataplexy. For example, DQB1-0601 is predictive for the appearance of narcolepsy-cataplexy [25], while a higher risk of cataplexy with EDS is seen in heterozygotes also expressing DQ B1-0301.

As mentioned, a large percentage of patients with cataplexy and EDS are DQ B1-0602, and the highest predisposing effect on the appearance of cataplexy associates the three locus haplotypes, i.e. , a combination of DR 15-0102, DQ A1-0102, DQ B1-0602. However, 8–10 % of patients with cataplexy and EDS will be negative for DQ B1-0602 but a high proportion of these patients will carry the susceptibility allele DQ B1-0301. In contrast, patients with EDS, two or more sleep-onset REM periods but no cataplexy will have a maximum of 40 % chance of carrying the major susceptibility allele DQ B1-0602. This indicates that narcolepsy-cataplexy is greatly influence by the presence/absence of specific HLA susceptibility alleles [26].

Genetic transmission is likely polygenic in most cases, and is tightly associated with the human leukocyte antigen (HLA) allele DQB1*0602, often in combination with HLA DRB1*15 (DR2) [15]. Month of birth is a proposed risk factor for development of narcolepsy (peak incidence in March and trough in September), with the suggestion that environmental factors acting in concert with genetic factors during the fetal or perinatal period may trigger autoimmune processes targeting the hypocretin (HCRT) system [27].

The major pathophysiology of human narcolepsy has been recently elucidated based on the discovery of narcolepsy genes in animals. Using forward (i.e. , positional cloning in canine narcolepsy) and reverse (i.e. , mouse gene knockout) genetics, the genes involved in the pathogenesis of narcolepsy (HCRT/orexin ligand and its recep-

tor) in animals have been identified [28, 29]. HCRTs/orexins are novel hypothalamic neuropeptides that are also involved in various hypothalamic functions such as energy homeostasis and neuroendocrine functions [30, 31]. Mutations in HCRT-related genes are rare in humans, but HCRT ligand deficiency is found in many cases [32, 33]. This recent discovery is likely to lead to the development of new diagnostic tests and targeted treatments. Since HCRTs are involved various hypothalamic functions, HCRT-deficient narcolepsy appears now to be a more complex condition than just a simple sleep disorder. Since HCRTs are involved in many hypothalamic functions, narcolepsy may be considered as more than just a disorder of sleep. In addition, it may be considered more as a syndrome of state instability than merely a disorder of dysfunctional REM sleep; patients have the capacity to reach wake, non-REM and REM sleep, but are unable to maintain the state. They appear to be lacking the modulator responsible for maintaining the active sleep state long enough for the normal physiological "switches" to change the state. Thus, patients with narcolepsy dissociate into the various states of consciousness at inappropriate times. This dissociation is often incomplete, leading to states of consciousness that are a mixture of normal states, i.e. cataplexy which represents a combination of the waking state and the paralysis of REM sleep [34].

Clinical features

The first symptoms often develop near the age of puberty; the peak age at which reported symptoms occur is 15–25 years, but narcolepsy and other symptoms have been noted as early as 2 years, and at 6 months of age in the case with HCRT gene mutation [35]. A second, smaller peak of onset has been noted between 35 and 45 years and near menopause in women.

Narcoleptic individuals experience EDS, usually associated with REM sleep phenomena, such as sleep paralysis, cataplexy (emotion-induced weakness), and hypnagogic hallucinations (visual, tactile, kinetic, and auditory phenomena occurring during sleep onset) [37]. Disrupted nocturnal sleep occurs frequently. Sleepiness is usually the first symptom to appear, followed by cataplexy, sleep paralysis and hypnagogic hallucinations [6, 37–40]. Cataplexy onset occurs within five years after the occurrence of daytime somnolence in approximately two thirds of the cases [38, 40]. The mean age of onset of sleep paralysis and hypnagogic hallucinations is also 2–7 years later than that of sleepiness [39, 41]. In most cases, EDS and irresistible sleep episodes persist throughout the lifetime.

EDS and cataplexy are considered to be the two primary symptoms of narcolepsy, with EDS often the most disabling symptom. The EDS most typically mimics the feeling that people experience when they are severely sleep deprived, but may also manifest itself as a chronic tiredness or fatigue. Narcoleptic subjects generally experience a permanent background of baseline sleepiness that easily leads to actual sleep episodes in monotonous sedentary situations. This feeling is most often relieved by short naps (15–30 min), but in most cases the refreshed sensation only lasts a short time after awaking. The refreshing value of short naps is of considerable diagnostic value.

Cataplexy has been considered pathognomonic of narcolepsy despite the fact that it can be seen, exceptionally, as an independent problem. Its isolated presence may lead to question whether daytime sleepiness also occurs. Its presence does not distinguish between primary and secondary narcolepsy. As already mentioned by Daniels [42], it consists of a sudden drop of muscle tone triggered by emotional factors, most often by positive emotions, more particularly laughter, and less commonly by negative emotions such as anger. In a review of 200 narcoleptics with cataplexy, all reported that laughter related to something that the person found hilarious, triggered an event; surprise with an emotional component was the second most common trigger. Cataplexy occurs more frequently when trying to avoid taking a nap and feeling sleepy, when emotionally drained or with chronic stress. Elderly subjects with very rare incidence of cataplexy may see a great increase in frequency during a period of grief such as loss of a spouse [43]. All striated muscles can be affected, leading to a progressive collapse of the subject. Most often the subject with complete collapse has the capability to avoid injury, as the fall is slow and progressive. Cataplectic attacks may be more limited. It may only involve head and neck, head, neck, and upper limb, more rarely lower limb with "knee buckling" [44]. The most common isolated form involves the facial muscles. It leads to a "trembling" of masseteric muscles, rictus, dysarthria, head and upper arm drop, and dropping of objects held in the hands [44, 45]. Sagging jaw, inclined head, drooping shoulders, and transient buckling of the knee may be the most common presentation. Slurred speech may be noted. Weakness of abdominal muscles and irregular breathing may occur but long diaphragmatic apneas have not been recorded.

The duration of the event is variable but is most often very short. A survey of 100 of our narcoleptics, age between 14 and 24 years, showed that 93 % of cataplectic events lasted less than 2min, with 96 % reporting events of 30 s or less duration, 6 % indicated events lasting up to 5min, usually when also sleepy. Just under 1 % (0.93 %) reported presence of events longer than 5 min.The age of onset of cataplexy is variable. In one of our studies of 100 teenagers and young adults (14–23 years) cataplexy was present simultaneously with EDS in 49 % of the cases, occurrence of sleepiness between 6months and 2 years after onset of sleepiness was seen in 41 % of subjects. Cataplexy developed between 2 and 6years after sleepiness in 4 % of subjects and preceded sleepiness by 0.5 to over 3 years in 6.0 %. Cataplexy, overall has a tendency to decrease with age.

Hypnagogic/hypnopompic hallucinations and sleep paralysis do not affect all subjects, are often transitory, and occur commonly in the general population [46]. Disturbed nocturnal sleep seldom occurs in the first stages and generally worsens with age [39].Narcolepsy is a very incapacitating disease. It interferes with every aspect of life. The negative social impact of narcolepsy has been extensively studied. Patients experience impairments in driving and a high prevalence of either car or machine-related accidents. Narcolepsy also interferes with professional performance, leading to unemployment, frequent changes of employment, working disability or early retirement [47–50]. Several subjects also develop symptoms of depression, although these symptoms are often masked by anticataplectic medications [47, 50, 51].

Several tests have been designed to objectively evaluate sleepiness. Yoss et al. [52] described the electronic pupillogram as a method of measuring decreased levels of sleepiness. Schmidt and Fortin [53] reviewed the advantages and limitations of the electronic pupillogram in arousal disorders. The multiple sleep latency test (MSLT) was designed to measure physiological sleep tendencies in the absence of alerting factors [54]. It consists of five scheduled naps, usually at 10 am, noon, and 2, 4, and 6 pm, during which the subject is polygraphically monitored in a comfortable, soundproof, dark bedroom, while wearing street clothes. The MSLT records the latency for each nap (time between lights-out and sleep onset), the mean sleep latency, and the presence or absence of REM sleep during any of the naps [55]. On the basis of polygraphic recording, REM sleep that occurs within 15 min of sleep onset is considered a sleep-onset REM period [56]. After each 20-min monitoring period, patients stay awake until the next scheduled nap.

An MSLT performed alone has the same drawbacks as does pupillography – it measures sleepiness regardless of its cause, which may simply be sleep deprivation. The MSLT also ignores repetitive microsleeps that can lead, in borderline cases, to daytime impairment not scored by conventional analysis. To be clinically relevant, the test must be conducted under specific conditions. Subjects must have abstained from medication for a sufficient period (usually 15 days) so that drug interaction is avoided. On the basis of sleep diaries, their sleep-wake schedules are stabilized. On the night preceding the MSLT, the subjects undergo a standard nocturnal polysomnogram. Throughout the total nocturnal sleep period, any sleep-related biological abnormalities responsible for sleep fragmentation and sleep deprivation are recorded. A nocturnal polysomnogram is useful for eliminating other possible causes of excessive daytime sleepiness such as periodic leg movements and obstructive sleep apnea. The diagnosis of upper airway resistance syndrome must also be very carefully considered. An MSLT is generally performed the following day. Sleep efficiency during nocturnal polysomnography may be normal or low.Browman et al. [57] proposed adding a test for the maintenance of wakefulness to the MSLT. This tests the patient's ability to remain awake in a comfortable sitting position in a dark room for five 20-min trials given at 10 am, noon, and 2, 4, and 6 pm. The test may be helpful in specific pharmacological trials, but has proved to be unsatisfactory as a diagnostic procedure [57]. Normally, the test consist of five nap opportunities placed at 2-h intervals similarly to the MSLT. Each opportunity for sleep lasts 20 min but some studies have claimed that prolonging each test to 30 min probably is better to dissociate pathology from normalcy.

In addition to these clinical and polysomnographic criteria, HLA typing showing the association with HLA DQB1*0602 is supportive of the diagnosis, but the specificity of DQB1*0602 positivity is low [58]. Today, cerebrospinal fluid (CSF) HCRT-1 measurement has become a major diagnostic tool in the diagnosis of narcolepsy and other hypersomnias [59, 60]. Low CSF HCRT-1 levels are very specific for narcolepsy when compared to other sleep or neurological disorders [60–62]. The establishment of CSF HCRT measurement as a new diagnostic tool for human narcolepsy is therefore encouraging.

The secondary narcolepsy-cataplexy

Association of cataplexy with EDS with another disorder of the brain was first reported in the early 1900. These associations includes tumors, localized most frequently to the diencephalon or to the brain stem, other diencephalic lesions (e.g. , large arterio-venous malformation, or lesions secondary to ischemic events), multiple sclerosis with plaques in the diencephalon, head injury, encephalitis, etc. In young children, Niemann-Pick disease type C, characterized by hepatosplenomegaly, progressive ataxia, dystonia, dementia and vertical supranuclear opthalmoplegia, is often associated with cataplexy early in life, as pointed out by Challamel et al. [63]. Cataplexy was noted much earlier in these children with Niemann-Pick, than in a group of prepubertal children [35] with a mean age of onset of 6years [63–66]. The other cause of very early onset of secondary cataplexy is craniopharyngioma. This tumor is one of the most common brain tumors in children and account for 9 % of all pediatric intracranial tumors (0.5–2 cases/million population per year) [67]. They often present between 5 and 10 years of age. As the tumors grow, they can involve the pituitary, optic chiasm, and the hypothalamus. They may lead to severe obesity, hypoventilation, and abrupt bilateral muscle weakness. Resection of the tumor often involves hypothalamic lesions and cataplexy and other symptoms may persist. If the craniopharyngioma has not invaded the hypothalamus, the surgical trauma related to the tumor removal may be responsible for a transient cataplexy that will recede progressively [68]. However, when cataplexy is present before surgery, removal of the tumor is not associated with regression of cataplexy. With the discovery of the HCRT/orexin system, and the possibility of measuring CSF HCRT-1 in patients with cataplexy, EDS and other symptoms associated with narcolepsy, several case reports or reports of short series of neurological lesions, mostly tumors, have documented that lesions of the lateral and posterior hypothalamus, independently of its mechanism, lead to lesions of HCRT-producing neurons associated with development of EDS and cataplexy [69–72]. Some cases may present a diagnosis challenge. As an example, hypothalamic astrocytoma leads to obesity, pseudo Pradder-Willi syndrome and associated atypical cataplexy. In this secondary cataplexy, the abrupt muscle weakness may not be triggered by laughter [72], and, depending on the onset of the neurological syndrome, may be seen very early in life (such as in Niemann-Pick type C) [63–66] or late in life. In one reprot, an association was demonstrated between the development of cataplexy with very little sleepiness and clinical symptoms of limbic encephalitis [73], in which an anti-Ma 2 antibody test was positive, and a further search revealed a testicular cancer. Neurological symptoms precede the diagnosis of cancer in 50 % of paraneoplastic syndromes. The presence of cataplexy out of the usual age range, the presence of atypical cataplexy, development of cataplexy without clear association with other symptoms of narcolepsy must raise suspicion, and further neurological and other evaluations are warranted to prevent a rare paraneoplastic syndrome or a primary cancer site being missed. That there can be an immunological involvement in the narcolepsy syndrome and paraneoplastic syndromes is an interesting observation.

Overall, however, secondary cataplexies are associated with specific lesions located in the lateral and posterior hypothalamus, involving the HCRT/orexin neurons.

These lesions can be seen at brain imaging. Occasionally, neurological lesions involve the brain stem, interrupting the descending pathways of the inhibitory reticular formation of Magoun and Rhine, responsible for maintenance of the active inhibition. Isolated cataplexy has been seen with a pontine pilocystic astrocytoma [74], variable EDS with brain stem glioblastoma [75], and subependynoma of fourth ventricle [76]. A 'status cataplecticus' was reported with a midbrain tumor [77].

Pharmacological studies

Systematic pharmacological studies have also been conducted in canine narcolepsy. Pharmacological studies performed in these animals suggest that both the cholinergic and monoaminergic systems are critically involved. The administration of cholinomimetic drugs known to increase REM sleep exacerbates cataplexy in narcoleptic dogs, while the administration of anticholinergic substances decreases cataplexy [78]. These results are similar to the facilitation of REM sleep obtained in animals after pharmacological increase of the central cholinergic transmission [79]. On the other hand, drugs that block the reuptake of noradrenaline have a powerful anti-cataplectic effect [80, 81], as opposed to dopamine-reuptake inhibitors, which seem to have little effect on canine cataplexy. Animal studies also looked at the pharmacology of α and β adrenergic receptors. α-1 adrenergic antagonists (prazosine, phenoxybenzamine) facilitated, whereas α-1 adrenergic agonists (methoxamine, cirazoline) suppressed cataplexy [82, 83]. Central dopamine D_2 agonists significantly suppressed cataplexy [84], whereas most D_2 agonists aggravated it; this suggests an involvement of "presynaptic dopamine receptors" in the regulation of canine cataplexy. However, experimental data suggest that the effect of D_2 compounds on cataplexy is probably mediated by the noradrenergic system [85, 86]. Dopamine-reuptake inhibitors have little effect on cataplexy, but exert a strong alerting effect [87, 88]. In fact, these compounds have little influence on REM sleep, but do produce a reduction of slow wave sleep and of total sleep time [87, 88].

These investigations indicate that a complex loop controls the appearance of canine cataplexy. Clear-cut differences in the activity of norepinephrinergic, serotoninergic and histaminergic cells are seen during canine cataplexy. Normally, all these cells are influenced by the HCRT neurons, with the locus coeruleus cells receiving predominantly, if not excessively, HCRT-1 excitation, while histamine cells have predominantly HCRT-2 influence. The fact that histaminergic cells carry on firing despite loss of HCRT neurons raises some questions, and suggests the existence of a non-HCRT-stimulating influence on these histaminergic neurons [89]. These findings must be integrated with recent reports by Willis et al. [90] and Kisanuki et al. [91], showing that cataplexy is more severe in ligand knockout and HCRT-1 knockout mice than in HCRT-2 knockout animals, which have worse sleepiness. This suggests a different impact of HCRT-2 and 1 on the symptomatology of narcolepsy, and the persistence of the activity of the histaminergic cells, appears to be responsible for that hybrid condition, i.e. , cataplexy with a muscle atony as in REM sleep and an awake cortex.

Treatments of narcolepsy

At the present time, there is no cure for narcolepsy, and treatment goals include control of EDS, cataplexy, hypnagogic hallucinations, and sleep paralysis; improvement of nocturnal sleep; and reduction of psychosocial problems.

Non-pharmacological measures target adherence to regular sleep and wake up time, multiple scheduled daytime naps of 15 min to 1 h, and avoidance of shift work. Career counseling is also important because patients and their employers must be educated regarding jobs that patients with narcolepsy should avoid. One of the most important initial treatments is a referral to patient support groups organized by sleep disorders centers, such as the National Sleep Foundation or the Narcolepsy Network. Other support groups exist in most Western European countries and in North America. The American Sleep Disorders Association is an integral resource.

Pharmacological therapy is directed towards symptomatic relief of EDS, REM sleep phenomena, and disrupted nocturnal sleep.

Pharmacological treatment of EDS with amphetamine-like compounds

EDS is usually treated using amphetamine-like CNS stimulants or modafinil, a novel wake-promoting compound unrelated to amphetamines. The most commonly used amphetamine-like compounds are methamphetamine, D-amphetamine, methylphenidate, pemoline, and mazindol. The most important pharmacological property of these compounds is to release catecholamines, i.e. , dopamine and norepinephrine. Amphetamine-like compounds also share the property of blocking the reuptake and the degradation of these monoamines (monoamine oxidase inhibition at high doses). All these properties presynaptically enhance dopamine transmission, which are likely to contribute to the EEG arousal effects of amphetamines.

The clinical use of stimulants in narcolepsy has been the object of an American Sleep Disorders Association (ASDA) Standards of Practice publication. Typically, the patient is started at a low dose, which is then increased progressively to obtain satisfactory results. This final dose varies widely from patient to patient. In adults, methylphenidate and amphetamines at dosages of more than 60 mg/day do not significantly improve EDS without the appearance of long-term side effects, including frequent worsening of the nocturnal sleep disruption. The drug is usually administered in three divided doses with a maximum of 20 mg in the morning, 20 mg at lunchtime, and 20 mg at 3 pm – never later. Therefore, short naps are necessary. The combination of pharmacological agents and two short naps provides the best daily response to EDS, with no stimulant drug taken after 3 pm. The slow-release form may provide gradual and delayed response during the daytime. Side effects such as headaches, irritability, nervousness, tremors, anorexia, palpitations, sweating, and gastric discomfort are common.

The introduction of two new agents has given more options to clinicians: modafinil (200–600 mg/day) and sodium oxybate (γ-hydroxybutyrate, GHB; 6–9 g/day). Modafinil is a CNS activating agent that has little or no effect on dopaminergic activity, but is histaminergic and has highly selective activity in the CNS relative to

amphetamines and methylphenidate [92, 93]. Although modafinil reduces subjective sleepiness and improves wakefulness in narcoleptic subjects, it does not reduce cataplexy. Modafinil has a low incidence of side effects, except for headaches, nervousness, nausea, and dry mouth. The most commonly used daily dose in open-label studies has been 400 mg (therapeutic range, 100–600 mg/day) in two divided doses (morning and lunch time). Modafinil can be administered concurrently with anti-cataplectic medications without problems. Despite the fact that all studies performed for approval by regulatory agencies were done on post-pubertal individuals, in an investigator-initiated study of 13 children (mean age 11.0 ± 5.3 years), modafinil at a dosage of 346 ± 119 mg/day reduced sudden sleep attacks in 90 % of the children, prolonged mean sleep latency (baseline 6.6 ± 3.7 min *versus* treatment 10.2 ± 4.8 min, $p = 0.02$), and appeared to be safe and well tolerated (mean treatment duration 15.6 ± 7.8 months) [94]. Modafinil may lower plasma estrogen concentration in women using oral contraceptives [95]. Therefore, dose adjustment of the contraceptives is advised.

Sodium oxybate (GHB) is a naturally occurring CNS metabolite that acts as a sedative to consolidate sleep. In addition to its use as an anti-cataplectic medication, it is also thought to be helpful in the reduction of EDS [96]. It is a naturally occurring metabolite of the human nervous system that is found in highest concentrations in the hypothalamus and basal ganglia. It has been shown to induce a normal sequence of non-REM and REM sleep in normal volunteers lasting 2–3 h at a dose of 30 mg/kg. The first trials on narcoleptics were performed in the late 1970s [97, 98]. GHB has also been part of multicenter studies in the United States [96]. The drug is normally taken at bedtime, while the patient is already in bed to avoid falls. A second dose is taken about 2 h after the first one, again while the patient is in bed. The effective dose has varied from 6 to 9 g, with an increase in total nocturnal sleep time and decrease in sleep paralysis, hypnagogic hallucinations, and nightmares. There is a progressive increase of dose intake over 6–8 weeks. The initial dosing is usually too low to have a therapeutic effect, particularly on sleepiness. This progressive effect indicates that the therapeutic effect is an indirect one. All patients subjectively reported progressive improvements in feeling rested upon awakening. Overall, a positive effect on cataplexy is reported. The response is gradual, with a significant decrease in the frequency of cataplectic attacks noted. As mentioned previously, this gradual effect means that other alerting agents must initially be given to patients to control sleepiness. If patients wake up in the middle of the night, they may be confused and disoriented, and they may have episodes of enuresis particularly at high dosages of 8–9 g. A transient worsening of cataplexy during the nocturnal period may occur. Nausea may be reported with a high dosage, as well as sluggishness in the early morning. Overall, patients prefer this drug to the anti-cataplectic drugs because there are fewer side effects.

Pharmacological treatment of cataplexy

Since the 1960s, it has been known that imipramine is very effective for reducing cataplexy [99]. Tricyclic antidepressants were the first drugs of choice, particularly protriptyline, but the anticholinergic effect led to impotence in more than 40 % of

male narcoleptics. Most tricyclic antidepressants with significant atropinic side effects are used as a last resource. Similarly, the monoamine oxidase inhibitors are rarely used except for the hybrid selegiline [100]. The newest agent, GHB, treats cataplexy through an unknown mechanism that is thought to be related to its consolidation of REM sleep [96–98, 101, 102]. Most medications used for cataplexy have a noradrenergic-reuptake blocker action. Viloxazine is available in Europe and is very effective in the treatment of cataplexy. The starting dose is 50–100 mg in two divided doses with a maximum dose of 200 mg/day [103]. The commonly used medications are the serotonin-reuptake blockers that have an active noradrenergic-reuptake blocker metabolite; these include clomipramine and its active metabolite desmethyl-clomipramine, fluoxetine and its active metabolite norfluoxetine, and zimelidine and its active metabolite norzimelidine [104, 105]. The newer antidepressants have also been found to be effective for cataplexy, sleep paralysis and hypnagogic/hypnopompic hallucinations. Venlafaxine (75–150 mg) has been the most widely used of these new compounds, both in adults and in children; it has shown good response and has less side-effects than the tricyclics, which are now used less often. Atomoxetine (10–30 mg) has been tried in cases of resistant cataplexy after failure of fluoxetine, other selective serotonin-reuptake inhibitor, and venlafaxine. Clinical trials of GHB have demonstrated the following: (1) dose-related efficacy against cataplexy and sleepiness with no acute rebound effect upon withdrawal after 4 weeks of therapy in a randomized, double-blind placebo controlled trial; (2) sustained increase in efficacy against cataplexy over 12 months with maintenance of efficacy against sleepiness, using a stable dose after titration; (3) maintenance of efficacy in patients maintained on GHB for 7–44 months; (4) dose-related increase in slow-wave sleep (stages 3 and 4 non-REM sleep), efficacy against sleepiness, and reduction in nocturnal awakenings at 7.5- and 9-g doses; (5) improvement in seven out of eight quality of life measures in the SF 36 questionnaire in an open label trial lasting 6 months; and (6) no negative effect on respiratory indices [96, 106–109, 100, 111]. GHB is becoming a drug of choice in treatment of narcolepsy and auxiliary symptoms in the USA, and it is complimented with modafinil to improve daytime alertness.

Shortcomings of current therapy

Partial efficacy

No single therapy addresses all of these symptoms. None of the medications currently available to combat daytime somnolence completely controls the "sleep attacks" associated with narcolepsy. Even optimal treatment with stimulants yields improvement to only approximately 60 % of normal sleep latency.

Side effects of therapy

Side effects are commonly seen with the various medications utilized, but more particularly with amphetaminic and tricyclic types of medications. Patients using a high dose of stimulants (defined as $>$ 120 % of the recommended maximum dose

by the ASDA) had higher frequency of psychosis, paranoia or disordered thinking, alcohol or poly-drug abuse, and psychiatric hospitalizations compared to patients using standard doses [112]. The presence of rebound hypersomnia is more frequent with higher dosages of amphetamines.

The use of stimulants during pregnancy in narcolepsy subjects has not been well studied but raises concerns regarding potential teratogenicity. The U.S. Food and Drug Administration (FDA) classifies drugs based on potential teratogenicity into five categories: (A) controlled studies have shown no risk to the human fetus in the first trimester and a remote possibility of fetal harm; (B) animal studies indicate no fetal risk, but no controlled studies in humans; (C) animal studies demonstrate either teratogenic or embryocidal effects with no controlled studies in humans; (D) there is evidence of risk to human fetuses, but benefits may make risks acceptable; (X) studies in animals and humans have demonstrated fetal abnormalities and the risks outweigh any possible benefit [113, 114].

Dextroamphetamine is a category D drug; methamphetamine, modafinil, and mazindol are category C drugs; and methylphenidate has no adequate animal studies and manufacturer suggests use if benefits outweigh risks. Pemoline is the only category B stimulant, and it carries a small, although significant, risk of hepatotoxicity. When the potential for teratogenicity is unknown, the benefits to the patient have to be weighed against the potential risks to the fetus; for many patients, it is suggested that stimulant use be discontinued or reduced during attempts at conception and for the duration of the pregnancy [115]. For the treatment of cataplexy, GHB is a pregnancy category B drug, while the antidepressants, such as venlafaxine, atomoxetine, and fluoxetine are category C drugs. As with stimulant use during pregnancy, the benefits to the patient have to be weighed against potential risks to the fetus.

Conclusion

Since most narcolepsy-cataplexy subjects (about 90 % of idiopathic cases), are HCRT ligand deficient, HCRT agonists may be promising in the treatment of narcolepsy. Cell transplantation, using embryonic hypothalamic cells or neural stem cells, and gene therapy (preprohypocretin /orexin gene transfer using various vectors) might also be used to cure the disease in the future. Narcolepsy is open for many new research protocols.

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Clinical Pharmacology of Sleep
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Sleep disturbances in restless legs syndrome (RLS) and periodic limb movements (PLM)

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Definition and historical notes

Restless legs syndrome (RLS) is a common, often under diagnosed, sensorimotor disorder characterized by an uncomfortable and disagreeable sensation in the limbs, especially in the legs, which provokes an overwhelming urge to move them. The symptoms appear or worsen during rest and are partially or completely alleviated by movement. This unpleasant feeling follows a circadian trend, occurring or intensifying in the evening or at night, making it difficult to fall or stay asleep. Due to its impact on sleep structure, the American Sleep Disorder Association has classified RLS as one of the causes of intrinsic insomnia.

The oldest report of the syndrome probably dates back to the 17th century, when the famous English physician Sir Thomas Willis described the restlessness of these patients as one "... of the greatest tortures". After about one century of silence, the symptoms were sporadically reported as one of the possible results of "nervous hysteria", using the curious term of *"anxietas tibiarum"*. It was only in the middle of the 20th century that, thanks to the Swedish Neurologist Ekbom, the syndrome gained the attention of the scientific world as a separate medical entity of neurological pertinence [1]. Ekbom created the term "restless legs syndrome," and performed the first epidemiological and clinical studies. He recognized the main secondary forms of RLS, observing a high prevalence of the symptoms in subjects who had undergone gastrectomy, in blood donors, in patients treated with neuroleptics, and in pregnant women. During recent decades, interest in the syndrome has increased a great deal among researchers, with significant consequences on the level of clinical aspects and therapeutic measures. RLS is a chronic disorder with rare periods of remission. The severity of symptoms varies extensively and usually increases with age. The patient's medical history and neurological examination are generally sufficient to diagnose the disorder. Hematological and instrumental investigations could be useful to differentiate between the idiopathic and symptomatic forms, and the polysomnographic study helps quantify sleep disruption and characteristic periodic limb movements (PLM). Notwithstanding the recent steps forward in understanding the mechanisms behind RLS, its pathogenesis remains unclear. Correct diagnosis is

Table 1. Clinical features of the RLS

Diagnostic features	
1.	An urge to move the legs usually accompanied or caused by uncomfortable and unpleasant sensations in the legs.
2.	The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting.
3.	The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching.
4.	The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night.
Supportive clinical features	
1.	Positive family history
2.	Positive response to dopaminergic therapy
3.	Presence of periodic limb movements (during wakefulness or sleep)
Associated features of RLS	
1.	Variable clinical course, but typically chronic and often progressive.
2.	Physical examination normal in idiopathic/familial forms.
3.	Sleep disturbance is a common complaint in more affected patients.

very important, given that we now have effective and well-tolerated pharmacological treatments that significantly improve the quality of life of RLS sufferers.

Epidemiology and clinical features

The publications of the International Restless Legs Syndrome Study Group (IRLSSG) in 1995 [2] and in 2003 [3] emphasized the four essential criteria together with supportive and associated features (Tab. 1), and these have been considered the international standard for the diagnosis of RLS. Diagnostic criteria are considered mandatory for definite diagnosis, while supportive clinical features may increase the probability of diagnosing RLS in doubtful cases, and associated features are common but do not contribute to the diagnosis.

Epidemiological findings

Recent epidemiological analyses of different populations, applying the International Diagnostic Criteria for RLS, have provided more detailed information and a prevalence rate ranging from 5 % to 15 % of the general population. Prevalence seems to increase with age, although reports of onset before 20 years of age are not uncommon in clinical studies [4, 5], and may decrease with age in elderly men and remain stable in elderly women [6]. There is a female preponderance ranging from 13 % to 17 % [6, 7]. Recent Asian surveys [8, 9] indicate a lower prevalence in those populations (1.5 % in Japan and 1 % in Singapore), but a larger body of data is necessary to

effectively show racial differences. Two recent large epidemiological surveys in the general population and in primary care reported new and interesting data. Among 4310 German participants (20–79 years) the overall prevalence was 10.6 %, increasing with age, and double in females compared to males. Interestingly, the risk of RLS increased evenly and the data confirmed the association with a lower quality of living for RLS patients [10]. In a small rural US primary care practice, 24 % of 2099 patients positively responded to the four essential criteria for RLS diagnosis, and 15.3 % reported suffering from the symptoms at least weekly [11]. Methodological issues and highly selected population may explain this high rate of prevalence. Elsewhere, in a Turkish population (3234 adults interviewed) a face-to-face study indicates a lower RLS prevalence (3.2 %), highlighting the frequency (mostly > 15 days/month) and the rate increasing with age, especially in males [12]. Prevalence estimates vary considerably probably because some epidemiological studies are based on clinical patient populations and are not representative of the general population. Moreover, the influence of variable genetic susceptibility or environmental factors may determine regional variations. Finally, different methodological tools (questionnaires, telephone interviews, direct observations) and different diagnostic criteria may explain some of these differences.

Clinical diagnostic features

An urge to move the legs usually accompanied or caused by uncomfortable and unpleasant sensations in the legs

Sometimes the urge to move is present without the uncomfortable sensations, and sometimes the arms or other body parts are involved in addition to the legs. Generally sensory and motor symptoms are present together in the same patient, but the sensory or motor component may prevail, creating some difficulties in explaining the symptoms: the sensations are usually described as something uncomfortable deep in the legs, usually between knee and ankle. From 30 % to 50 % of RLS patients may complain of sensations involving the arms, although symptoms in the arms only, without involving the legs are rare and atypical, as is extension to other parts of the body. The presence of only an urge to move without sensory symptoms is unusual but may occur [3].

The urge to move or unpleasant sensations begins or worsens during periods of rest or inactivity such as lying or sitting

This criterion describes the typical arrival of symptoms when the period of rest is prolonged, and there is an increase in sensations and the urgent need to move the legs. These typical features emerge during long rest periods, lying down in bed in the evening, and made it possible to come up with a test that reflected the increase in the severity of sensory symptoms and urge to move with the length of the rest or immobile period (Suggested Immobilization Test, SIT) [13].

The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues
Generally, the relief brought about by movement is immediate and lasts as long as the activity continues. Different activities may lead to a reduction in RLS symptoms, but all patients are aware that some are better than others in providing relief: walking, stretching, massages or other actions such as hot or cold baths or putting the legs under the shower provide the most typical relief for the symptoms. In contrast, physical activity during the day, even if intense and prolonged generally does not achieve the same effect, and in many cases may exacerbate the evening/night symptoms.

The urge to move or unpleasant sensations are worse in the evening or at night than during the day, or only occur in the evening or at night. When symptoms are very severe, the worsening at night may not be noticeable but must have been previously present. The circadian effect on RLS is well documented by the reports of patients even when the symptoms are also present during the day. It seems independent from the rest and recumbent position, and it is also applicable to PLM [14]. Recent studies on circadian variation of RLS and PLM during sleep (PLMS)/PLM during wakefulness (PLMW) confirmed previous findings on prevalence between midnight and 4 am (acrophase at 3 am) and a decrease from 6 am to noon (acrophase 10–11 am) [15]. The profile of variations in leg discomfort and PLM correlate with core body temperature and salivary melatonin: most PLM occur during the falling phase of circadian temperature curve and the lowest number during the rising phase [14, 15].

Supportive clinical features

Positive family history of RLS
Different clinical and epidemiological studies indicated that more than 60 % of RLS patients have a positive family history for RLS, at least for primary forms [16–18]. A definite or possible positive family history was found in 54.9 % of patients with idiopathic RLS, but in only 17.5 % of patients with RLS associated with uremia [17]. Bimodal distribution seems to be associated with distinct etiological and clinical features: primary form, familial pattern, mild and slow progression for early onset, and secondary/primary form, sporadic pattern, moderate to severe form and frequent low serum ferritin for late onset [19]. Segregation analysis of families suggests that those families where individuals experience early onset (mean onset before age 30) demonstrate a pattern of familial distribution most consistent with a dominant inheritance [19]. Genetic linkage studies found both recessive and dominant models of inheritance [20–22] with different disease-susceptibility loci on chromosomes 12, 14 and 9. It seems very likely that other linkages will be located, and most consider that RLS will turn out to be a genetically 'complex disorder' with heterogeneity in inheritance and different potential contributing genes, most with small effects and whose importance may vary from population to population [23].

Response to treatment
Several controlled studies [24–30] have shown that most people with RLS have a positive therapeutic response to dopaminergic drugs. These medications improve

both the sensory and motor symptoms of RLS. The drugs included the precursor of dopamine [24, 25] and dopamine-receptor agonists [26–30]. Based on clinical experience, more than 90 % of patients report some relief of their symptoms when treated with these agents. The positive response at a very low dose of medication indicates that when dopaminergic agents are effective, the diagnosis of RLS is confirmed. It is still necessary to define whether mimic disorders (neuropathic pain syndromes, painful legs and moving toes, leg akathisia or generalized akathisia; nocturnal leg cramps, propiospinal myoclonus, neuropathies, radiculopathies,) are also responsive to these drugs [23].

Periodic limb movements

PLMS has been classically described as a rhythmic extension of the big toe and dorsiflexion of the ankle, with occasional flexion at the knee. A PLMS index (number of movements per hour of sleep) of more than 5 present in at least 80–90 % of RLS cases during at least one of two nights of sleep recording and a PLMS index of 11 on either of the two consecutive nights of recording provide the optimal sensitivity and specificity for a diagnosis of RLS [31, 32]. This study demonstrated the night-to-night variability in the PLMS index and, therefore, the advantage of recording PLMS over several nights. Future developments in activity meters to measure PLMS may facilitate the recording of PLMS over several nights and may thereby enhance the value of this measure for supporting the diagnosis of RLS. Research results from the polysomnographic studies have shown that people with RLS frequently have PLMW. Using the SIT, the presence of PLMW in RLS patients can be considered as supporting the diagnosis [32]. Although the presence of PLMS is not RLS specific, an elevated PLMS index also supports RLS diagnosis. During both the sleep period (WASO) and the SIT, PLMW appear to be more specific for RLS, but the data for this finding remain limited [13, 33]

Associated features of RLS

Natural clinical course of the disorder

The age of onset of RLS is known to vary from childhood to more than 80 years of age [34–37]. RLS is generally a chronic condition, but it may have different phenotypic patterns of expression: mild, occurring less than once a week or even once a month, variable with long periods of remission and sometimes only occurring for a limited time of life, waxing and waning of symptoms depending on the season or the condition of the patient, moderate to severe, occurring frequently up to every evening/night. For patients who begin experiencing RLS in their young adult life, the severity and frequency of symptoms typically increase over time [34]. No long-term follow-up studies are available to establish the natural history of RLS both for primary and secondary forms. Those with disease onset in late adult life have been found to have a generally more rapid development of symptoms and to have no clear correlation between symptom severity and age [36, 37].

Sleep disturbances

These refer to the subjective experience of disrupted sleep, including difficulty in falling asleep, reduced sleep time, increased amount of awakening with symptoms. Thus, RLS presents two problems for sleep: falling sleep and staying sleep. Insomnia may be the only symptom that patients report because many of them do not realize that the sensory symptoms or the urge to move is the main cause for finding it hard to fall asleep or for waking up. For patients with mild RLS, sleep disturbance may be less of a problem. Sometimes patients have disturbances during the day in forced-rest conditions and slight symptoms right at the time of falling sleep, but their presence increases at night awakenings. Others describe some mild symptoms at sleep onset, which easily resolve with small movements or cease when the patients fall asleep. Even with successful treatment of the symptoms, patients with RLS may continue to have sleep problems, perhaps due to learned responses or classical conditioning leading to insomnia [37].

Medical evaluation/physical examination

A neurological examination is normal in patients with the primary form of RLS, but patients with late-onset RLS symptoms and secondary forms may show evidence of a peripheral neuropathy or radiculopathy [38]. Apart from the established causes of secondary RLS, there are no known physical abnormalities associated with RLS. A low to normal serum ferritin level (45–50 mg/L) has been related to increased severity of RLS, and may be associated with an increased risk of the occurrence of RLS even in patients with normal hemoglobin levels [37, 39]. Therefore, evaluations of serum ferritin levels and percentage of iron saturation are highly recommended as part of the medical evaluation for RLS.

Secondary RLS and associated pathologies

Among the pathologies associated with RLS, several groups [38, 40] have reported neuropathies and radiculopathies. Evidence of peripheral axonal neuropathy of a mild degree was found in some putative idiopathic RLS patients through electrophysiological (EMG/NCV) and psychophysiological tests, subsequently confirmed by sural nerve biopsy [41]. These data have recently been confirmed in 30 % of 22 patients by means of skin biopsy, and related to late onset associated with pain-like symptoms [42].

Rheumatoid arthritis has been reported to be associated with RLS in up to 25 % of cases [43], but serological analysis of 68 RLS patients failed to find association with rheumatological serologies [44]. The same holds true for diabetes, often reported in association with RLS; however, a recent extensive clinical study did not find a significantly higher prevalence of RLS in diabetic patients [44]. Neuropathies associated with rheumatoid arthritis and diabetes may be the cause of RLS in these patients. In patients with end-stage kidney disease, reports showed a mild or overt (from moderate to severe) RLS in up to 62 % of cases [45, 46]. No correlation with iron levels or other uremia characteristics such as a decrease in parathormone levels has been found [46]. Parkinson's disease (PD) has frequently been associated with

RLS, and studies have pointed to the efficacy of dopaminergic treatment for both pathologies. A recent study by Ondo et al. [47] found that 20.8 % of 303 PD patients met RLS diagnostic criteria. In contrast, a similar study conducted in Singapore among 125 PD patients did not find any case satisfying IRLSSG criteria for RLS [48]. There are no clinical studies associating RLS with myelopathies; only case descriptions have reported RLS concomitant with lesion of the spinal cord. de Mello et al. [49] found a high frequency of RLS and PLMS in spinal cord injuries (T7–T12), with symptoms attenuated after physical activity. PLMS have frequently been reported in association with spinal cord lesions, irrespective of the nature of the lesions. We detected PLMS in 36 % of 25 patients with multiple sclerosis, correlated with high magnetic resonance imaging lesion loads in infratentorial regions [50]. Iron metabolism has been extensively evaluated in RLS, in particular by the Johns Hopkins Group in Baltimore [36, 37, 51, 52]. There is a frequent association between RLS, anemia and low serum levels of ferritin [36, 51, 52]. Recent research has shown low ferritin levels and high transferrin concentrations in CSF of patients with RLS, sometimes despite high or normal serum iron levels, suggesting an alteration of blood-brain barrier transport [51]. Pregnancy may induce RLS symptoms or make a pre-existing form of RLS worse. Pregnancy-related RLS usually reaches the highest severity during the third trimester and tends to disappear around the time of delivery. The reasons for the association between pregnancy and RLS are unclear. Since the iron and ferritin levels physiologically decrease in late pregnancy, and lower values of plasmatic iron storage indicators have been demonstrated in pregnant women with RLS, compared to unaffected pregnant women, the pathogenetic role of iron in this RLS form has been put forward [53].

Pathogenic hypotheses

Neurophysiological methodologies represented the first significant approach in trying to understand the mechanism of RLS. While common examinations, such as the standard electroneuromyography, yielded results that were normal in idiopathic RLS, more sophisticated analysis revealed mild abnormalities in both sensory and motor systems. Studies by transcranial magnetic stimulation and blink reflex test disclosed a generic hyperexcitability of the motor outflow in RLS patients [54, 55]. Since PLM closely resembles the triple flexor reflex to the pain, it has been suggested that this motor facility could be the result of a disinhibition of the upper nervous structures to the spinal centers. The facts observed by the flexor reflex studies in RLS patients seem to support this theory [56]. On the other hand, the sensory system also seems to be involved in RLS pathogenesis. Quantitative sensory testing showed an impairment of temperature perception in a high percentage of idiopathic RLS patients [57]. Although these studies supported a central origin of sensory impairment, it is in fact unclear whether these deficits are caused by peripheral nerve damage or by a dysfunction in central somatosensory processing. Further interesting information has emerged from the symptomatic forms of RLS. The high prevalence of RLS among subjects with iron deficiency, together with the negative correlation existing between ferritin serum

levels and RLS severity, suggest that the iron metabolism is a significant factor in RLS pathophysiology [37]. Reduction of iron in the substantial nigra, as of ferritin in cerebral spinal fluid, has been found in RLS patients [51, 52]. Moreover, iron supplements could be a possible therapeutic solution in specific cases [37]. The low brain iron and ferritin concentrations, also in patients with normal serum levels, and the reduction of transferrin receptor on the neuromelanin-containing cells, suggested a possible dysfunction of iron transportation from serum to central nervous system, or an impairment of iron acquisition in neuromelanin cells [58]. RLS is particularly frequent during the third trimester of pregnancy [53]. This finding is consistent with either the iron theory, because serum iron indicators reach the lowest levels during this phase of pregnancy, or a hormonal theory, since the syndrome seems to be more prevalent in females than in males, and generally in women taking estrogen-based contraceptives. Estrogens, as well as progesterone, increase markedly during late pregnancy.

Since low doses of dopaminergic drugs have shown a surprising beneficial effect in relieving RLS symptoms, several researchers switched their attention to the dopaminergic system, to investigate a possible key role of dopamine in RLS pathogenesis. Besides the pharmacological facts, other data consolidated this hypothesis. PLM and RLS are often noticed in patients affected by PD [59], and in subjects chronically treated with anti-dopaminergic drugs such as neuroleptics. The occurence of RLS symptoms hits a maximum at night when dopamine levels are lowest, and when melatonin, which inhibits the central dopamine secretion, reaches its highest value. Motor hyperexcitability has been induced in animal models by lesion of the hypothalamic dopaminergic neurons, which project to spinal centers [59]. Furthermore, the iron and hormonal hypothesis mentioned above could comply with a dopaminergic dysfunction. Iron is a key coenzyme in the dopamine anabolism, and estrogens have an anti-dopaminergic effect at the basal ganglia [60, 61]. Data from SPECT and PET analysis showed ambiguous results regarding a possible dopamine deficit in basal ganglia of RLS patients [62]. Although an impairment of the dopaminergic system seems to be likely in RLS patients, the primary causes underlying the mechanism of RLS are currently unknown, and further investigations, especially in the field of genetic and animal models, are needed to clarify RLS pathophysiology.

Sleep disturbances and periodic leg movements in RLS

Because of the increase in symptoms at rest and at night, RLS has an important impact on sleep induction and maintenance. Besides the classic difficulty in falling asleep because of the sensory symptoms accompanied by the urge to move legs, and the reappearance of RLS during nocturnal awakenings, once asleep 80–90 % of patients present PLM. PLM are repetitive limb movements that usually occur during sleep (PLMS) [63], but can also occur while individuals are awake (PLMW), especially in patients with RLS [64]. PLM are defined by their occurrence in a series (four or more) of similar movements with a wide range of periods (5–90 s) and duration of 0.5–5 s. It has recently been proposed that PLMW bursts can be longer lasting (up to 10 s),

perhaps due to a voluntary prolongation of an initially involuntary movement [65]. The movements involve both legs in almost every case, but they may predominate on one side or alternate between legs during the night, and sometimes the arms may also be involved [66]. PLM are more common in NREM sleep, in particular in light stages 1–2 NREM, but frequently, and more often in severe RLS, they may appear also in slow-wave sleep (stages 3–4 NREM) and in REM sleep (shorter in duration and with a more irregular inter-movement interval). Since their description by Symonds [67] and Lugaresi et al. [68, 69], epidemiological and polysomnographic studies have shown that PLM are extremely common also in subjects not affected by RLS, especially in the elderly, more than half of whom may have more than five per hour of sleep (PLMS Index, > 5) [70, 71]. Moreover, PLMS appear nonspecifically in other sleep or neurological pathologies, such as REM behavior disorder [72], narcolepsy [73], sleep breathing disorders [70], PD [74], and multiple system atrophy [74]. PLMS have also been found in patients with uremia, multiple sclerosis, radiculopathy, transection or compression of the spinal cord, and they may develop in patients treated with drugs such as neuroleptics or dopamine antagonists, antidepressant as serotoninergic agents or metclopramide. PLM are usually rated as the number of events per hour of sleep, and an index of more than 5 is commonly considered significant. Currently, it is controversial as to whether they cause a sleep disorder on their own (which would be called PLM disorder or PLMD) [75–77]. These myoclonic jerks are recorded by surface EMG of both tibialis anterior muscles during polysomnography (PSG), and are frequently associated with autonomic/EEG arousals or awakenings. They contribute, especially in RLS, to sleep fragmentation, affecting either its macro- or microstructure. The detection of the number of PLMS associated with arousals and calculation of the cyclic alternating pattern rate during NREM sleep, are the most widespread methods to quantify the impact of RLS on sleep [78]. The link of PLM to these cyclic phenomena also suggests that they are part of an extensive system of rhythmically modulating internal states [79, 80]. The long sleep latency, the difficult in returning to sleep after awakenings combined with frequent awakenings or arousals associated with PLMS lead to a very reduced sleep time (Fig. 1). Unlike patients with other sleep disorders and sleep deprivation, patients with even severe RLS do not generally report problems with uncontrollable sleepiness in the daytime.

The presence of PLMW in patients with RLS provided the basis for a physiological test that is more specific to RLS than PLMS: the SIT. During this 60-min test, patients lie in bed at a 45° angle with eyes open and legs stretched out. PLM are recorded the same as during PSG, together with EEGs to ensure the state of wakefulness. In this test, the subject is asked to sit quietly, typically between 9.00 and 10.00 pm, while leg movements and subjective complaints are monitored. Most patients with RLS will experience greater sensory discomfort than normal and will also undergo a fair number of movements during this period, which fulfill criteria for PLMW [81].

PLM can also be detected using a more recently developed technique, actigraphic monitoring. This technique is not identical to the standard EMG monitoring, since actigraphs record movement and not electrical potentials [82]. The advantage of actigraphy is that it is much less expensive than PSG, can be conducted in any

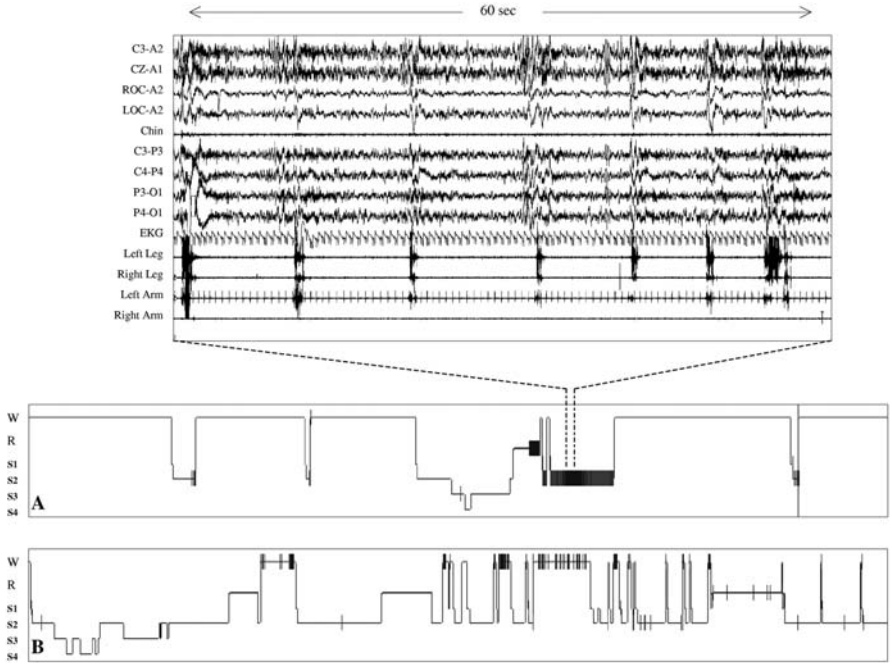

Fig. 1. Sleep histogram of a Polysomnography (PSG) in a RLS patient with PLMS before (A) and after (B) dopaminergic treatment. For PSG: C3-A2, CZ-A1, C3-P3, C4-P4, P3-O1, P4-O1 are EEG derivations. ROC (Right outer canto)-A2 and LOC (left outer canto)-A2 for electrooculogram. Chin for Submental EMG. Left leg, right leg, left arm and right arm for left tibialis anterior EMG, right tibialis anterior. EMG, left biceps EMG, right biceps EMG, respectively. W, wakefulness; R, Stage REM; S1, stage 1 NREM; S2, stage 2 NREM; S3, stage 3 NREM; S4, stage 4 NREM.

environment, and is relatively easily used on a long-term basis. The disadvantage is that actigraphy provides less information about the context of movement [3]. Actigraphy can also be used to assess RLS [37, 82–85], examining activity profiles, which are elevated during the evening and night hours [23, 86, 87]. Because of the lack of discrimination between sleep and wakefulness, the raw measure of activity during the night may include sleep movements (such as PLMS) and wake activity (such as PLMW or any other leg movement) [85].

PLMS, PLMW and leg sensory discomfort have a similar circadian profile, as do subjective complaints of RLS patients. The changes in melatonin secretion preceding the increase in sensory and motor symptoms in RLS patients seem to suggest that melatonin may be implicated in a worsening of RLS in the evening and at night, through a possible inhibitory effect on central dopamine secretion [15].

Non-pharmacological and pharmacological treatment of RLS and PLM

Non-pharmacological and iron treatment

Before considering the pharmacological option, it is essential for the physician to rule out a possible secondary origin of the syndrome. Removing or controlling possible etiological factors should be the first approach to treatment. Often RLS symptoms could be provoked or worsened by other chronic medications as antipshycotic, antidepressant or dopamine-blocking antiemetics. In these cases, where feasible, the accused drug should be withdrawn, decreased in dosage, or administered during the early part of the day. In depressed patients who require treatment, bupropion may be considered, since it has a beneficial effect on PLM. Pregnancy-related RLS is a benign form, which generally disappears after delivery. For this reason and because of the lack of studies on the safety of the current RLS therapy in this condition, drug treatment in pregnant women is usually not recommended. Systemic or lumbar anesthesia could trigger RLS, but also here symptoms are typically transient and drugs are not necessary. In symptomatic RLS forms associated with peripheral neuropathies, renal failure, rheumatoid arthritis, or other sleep disorders such as narcolepsy, obstructive sleep apnea or primary insomnias, the initial approach has to be focused on the causes.

In both primary and secondary forms, beginning a drug therapy should be evaluated also on the basis of the severity of RLS. Overall, many patients need no specific medications during the early stage of the disease because of the low frequency or intensity of the symptoms. In these subjects, a few behavioural suggestions or an intermittent drug therapy could represent a valid alternative. Patients affected by RLS should avoid or reduce alcohol, nicotine or stimulants. In situations that exacerbate the symptoms, such as boredom or periods of forced rest, especially in the evening and at night, activities to keep the mind alert can be helpful.

The demonstration that iron deficiency was an important risk factor in RLS pathogenesis has led, since the 1950s, to several therapeutic attempts with iron supplements. Initially, these attempts were aimed at subjects with RLS and hyposideremia, with or without anemia; later partial supplementation was also tested in patients with the idiopathic form.

A single intravenous infusion of 1000 mg iron dextran has also been evaluated in two open label studies, in which idiopathic RLS patients ($n = 11$) in the one study, and RLS patients with chronic kidney failure ($n = 25$) in the other study, were included [88, 89]. In both investigations, a therapeutic effectiveness was reported for a period of 2–4 weeks, and in one study the authors also noticed a reduction in PLM [88]. The results from oral iron therapy seem to be less convincing. In the only double-blind study available in literature, 24 RLS patients were treated for 2 weeks with a daily amount of 325 mg of iron sulfate. Despite the fact that a considerable number of the subjects did not complete the study due to the appearance of side effects, no significant difference in symptom relief was reported between treated and control group. Reduced effectiveness of oral iron therapy could depend

on the variability of gastrointestinal absorption. Moreover, iron acquisition could also depend on the pre-existing ferritin values, being significant in hyposideremic patients and negligible in non-hyposideremic subjects. On the basis of these few data, parenteral iron therapy could be considered as a possible alternative after the first-choice treatments, irrespective of the ferritin values; oral iron supplements should be reserved for patients with ferritin levels of less than 45–50 μg/mL. In these cases the therapy consists of 325 mg iron sulfate three times a day, possibly together with 100–200 mg vitamin C to increase absorption. The frequent occurrence of intestinal intolerance limits oral iron supplements, and severe allergic reactions can complicate intravenous infusion.

Pharmacological treatment

Drug treatments of RLS and PLM have to be considered together, and to date there are four identified classes of medications: dopaminergic agents, opioids, benzodiazepines (BZDs) and anticonvulsants [83, 84, 90, 91].

Dopaminergic agents
This first-line treatment includes L-dopa and dopamine agonists (DAs). L-Dopa (50–200 mg, plus dopa-decarboxylase in standard or sustained release preparation) was the first and best studied drug with rapid effectiveness; however, partly due to the short half-life, it also leads to a rapid development of augmentation (occurrence or worsening of RLS symptoms earlier in the day, with a possible increase in severity and involvement of other body parts) or early morning rebound of symptoms, particularly with higher doses and long-term usage [24, 25, 83]. DAs are preferred due to the longer half-life and fewer management problems in long-term use and for patients with moderate to severe forms. Both D2 and D3 receptor agonists are effective, while none of the effective drugs seems to have an effect on D1 receptors. Pergolide (0.25–0.75 mg), pramipexole (0.25–1.0 mg), ropinirole (0.25–4.0 mg), bromocriptine (1–10 mg), and cabergoline (0.5–3 mg) yeild convincing data for a positive effect both on sensory symptoms and PLM [84]. In general, starting with the lower dosage and up-titration to the effective doses should prevent side effects both for ergot (nausea, fatigue, headache, congestion, rare fibrosing reactions) and non-ergot (nasal stuffiness, insomnia, peripheral edema, nausea) drugs. Augmentation is less common with these agents that with L-dopa, but may occur in a third of patients with short or intermediate half-life drugs, although rarely with the long-term cabergoline [85, 92]. Since the doses are much lower and given once a day (1–2 h before bedtime) than in PD, daytime sleepiness or sleep attacks appear rare. Other dopamine agonists, which are probably effective but for which less evidence is available to date, are talipexole, rotigotine, piribedil, alpha-dihydroergocryptine, amantadine and selegiline.

Opioids
Among the opioids, controlled studies are limited and only reports on single cases or on a few patients are available. They showed a positive response of RLS to analgesic

opioids such as propoxyphene (50–500 mg), codeine (30–60 mg), oxycodone (5–20 mg), morphine (0.1–0.5 mg/day, intrathecal), methadone (5–30 mg). No formal comparison among the different compounds has been tried. Opioids given intrathecally via infusion pump have also been reported to improve severe and resistant cases of RLS. Apomorphine, through its dopaminergic and its opioidergic activity, has proved to be effective in idiopathic and symptomatic RLS as well as in PLM disorder when given intravenously or subcutaneously. Tramadol (50–100 mg), a narcotic with a nonopioid mechanism of action may be effective [83].

Benzodiazepines

Benzodiazeprines may be effective in improving RLS by direct action on sleep structure, but their use is limited by daytime and night-time side effects (sedation, hypotonia), especially in older patients. Clonazepam (0.5–2.0 mg), temazepam (15–30 mg), triazolam (0.125–0.25 mg) are the best studied drugs and these also have a limited effect on PLM. However, inappropriate use, psychological dependence, and physiological tolerance are limitations in the use of this drug category. Recently, non-benzodiazepine short-term hypnotics, such as zolpidem 5–10 mg, zaleplon 10–20 mg and zopiclone 10–20 mg, have been proposed to help nocturnal RLS symptoms. A few uncontrolled studies involving a small population of middle- and late-onset patients indicated an effect on sleep and RLS symptoms. These drugs, as well as other hypnotic agents, may be useful in combined treatment of RLS and insomnia when, despite disappearance of sensory and motor symptoms, sleep is still unstable or absent [83].

Anticonvulsant

Among the anticonvulsants, the most promising and effective is gabapentin, a modulator of various receptor sites and with properties that alter dopamine, serotonin and norepinephrine release. It showed positive response in idiopathic and symptomatic (hemodialysis, PD and dementia patients) RLS, in particular in painful or in neuropathic forms. The dosage range is 100–300 mg initially, increasing up to 1300–1800 mg once or twice a day. Limitations are sleepiness and unsteady gait especially in the elderly; therefore, 300–900 mg doses have been used, and appear to benefit RLS and PLM in most of the patients. Carbamazepine has been shown to be effective mainly for sensory symptoms, as has valproate, notwithstanding the possible side effects (sedation and weight gain) [83].

Other possible alternative drugs showing at least some effects are clonidine (used also in children and in uremic patients) and baclofen (with effect on PLMS reducing the arousal response to movements) [83].

Considering treatment in special populations, clonidine, dopamergic agents and gabapentin may be considered in end-stage renal disease; in pregnancy no drug currently used to treat RLS or PLM is considered completely safe: only some dopaminergic drugs, such as pergolide, or opioids, such as oxycodone, may be considered a lower risk, while L-dopa, pramipexole or gabapentin should be used only in the very severe form because of the higher risk. In children treatment should include strict sleep hygiene and medications only when diagnosis is definite and symptoms and

consequences are frequent; clonazepam, L-dopa, DAs and clonidine are the drugs with small studies showing positive results.

A recent algorithm of the management of RLS has been product by the Medical Advisory Board of RLS Foundation, indicating some guidelines for different forms of RLS [93]; summarizing these briefly: for intermittent RLS, iron replacement if iron levels are low, activities to keep the mind alert, abstinence from caffeine, nicotine and alcohol, discontinuation of eventual drugs that may potentially bring on symptoms, and intermittent use of L-dopa, pramipexole, ropinirole, tramadol, or benzodiazepines. For daily RLS, DAs, gabapentin, or low-potency opioids. For refractory RLS treated with DA but with inadequate response, intolerable side effects or augmentation: change to gabapentin, change to a different DA (i.e. , long half-life cabergoline), add a second agent such as gabapentin, a benzodiazepine or an opioid, change to a high potency opioid or tramadol.

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Sleep disturbances in anxiety disorders

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Sleep disturbances in anxiety disorders

Anxiety disorders are one of the most common mental disorders associated with sleep disturbances. A survey of US adult showed 24% of patients with insomnia, and 28% of patients with hypersomnia carried a diagnosis of anxiety disorder [1]. A large survey in France also showed that about 41% of patients with insomnia complaints had a current diagnosis of anxiety disorder [2].

Anxiety and fear states are characterized by heightened cortical and peripheral arousal. Hyperarousal of the autonomic or central nervous systems is also thought to disrupt sleep and may result in insomnia [3, 4]. Therefore, the high prevalence of sleep disturbances in anxiety disorders is not a surprise. In fact, sleep disturbances are included among the diagnostic criteria of two of the categories of anxiety disorders [i.e. , general anxiety disorder (GAD) and post-traumatic stress disorder (PTSD)], and are associated features in some of the other categories [5]. The anxiety disorder is usually presumed to be the cause of the sleep disturbances in patients with both conditions. In one study, for example, anxiety appeared before or concurrent with the sleep symptoms in about 80% of anxiety disorder patients with insomnia symptom [6]. However, it is still difficult to judge the causal relationship between sleep and emotional disturbances in clinical patients. For example, even when a patient's symptoms of anxiety predated the onset of sleep disturbances, the insomnia may be secondary to the anxiety disorder but sleep-specific pathologies (such as poor sleep hygiene and worries over poor sleep) may have developed later on and exacerbated the disturbed sleep. It is also possible that a third factor (such as stress) leads to both the anxiety disorder and sleep problem.

In this chapter, we present the findings on subjective reports and objective measures of sleep and sleep disturbances in patients with anxiety disorders. The im-

plications of these sleep findings on the etiologies of the anxiety disorders is also discussed. In addition, we summarize the current pharmacological and nonpharmacological approaches for the management of sleep disturbances in patients with anxiety disorders. Since the different categories of anxiety disorders share a common feature of excessive level of fear or anxiety, they may have some shared pathologies. However, the diagnoses are also different in many aspects. Therefore, the discussions are separated for different diagnoses. Since there are very few studies focused on the sleep of patients with specific phobias and acute stress disorder, these two disorders are not included in our chapter.

Sleep and sleep disturbances in anxiety disorders

Sleep and sleep disturbance in generalized anxiety disorder

Sleep disturbance is included as one of the diagnostic features of GAD. GAD is characterized by generalized and persistent symptoms of anxiety that are driven by worry, which lasts for at least 6 months. The diagnosis of GAD requires the presence of three of the six anxiety-associated symptoms, including easily fatigued, restlessness, poor concentration, irritability, muscle tension, and sleep disturbance [5].

Survey studies have shown that about 50–70% of patients with GAD experience sleep disturbances [7–9]. Similar to primary insomnia, common sleep complaints in GAD are difficulty falling sleep, difficulty staying asleep and restless and unrefreshing sleep. Their sleep disturbances often become a subject of their obsessive worry, particularly around bedtime. Although nightmares are not one of the most common sleep complaints in GAD, one study showed that the frequency of disturbing dreams was associated with GAD symptoms in adolescences [10]. Several studies have examined sleep in GAD patients with polysomnographic (PSG) recordings. In general, the findings were consistent with the patients' subjective complaints. PSG sleep of drug-free GAD patients are characterized by increased sleep onset latency, increased wake time after sleep onset, reduced total sleep time, and decreased sleep efficiency when compared to healthy individuals. The distribution of different sleep stages across the night, however, did not show remarkable and consistent abnormalities across studies [11–13].

Sleep and sleep disturbance in panic disorder

Patients with panic disorder suffer from episodes of acute anxiety associated with several somatic symptoms such as tachycardia, chest pain, heart palpitations, and gastrointestinal discomfort, accompanied by the impression that they are going to die. Patients are diagnosed as panic disorder with agoraphobia when they have "anxiety about, or avoidance of, places or situations from which escape might be difficult (or embarrassing) or in which help may not be available in the event of having a panic attack or panic-like symptoms" [5]. Panic attacks may occur during the daytime as well as during sleep.

The studies on subjective sleep complaints in patients with panic disorder have not obtained consistent results. One study showed that 68% of patients with panic disorder reported moderately to severely impaired sleep, compared to only 15% of healthy controls, and 26% of panic disorder patients complained of frequent awakenings, compared to none in healthy controls [14]. Another study, however, did not find significantly higher rate of sleep complaints in patients with panic disorder than in normal controls [15]. The findings on PSG sleep in patients with panic disorder are also not consistent across studies. Different PSG sleep features found included increased sleep onset latency, decreased total sleep time [16, 17], decreased sleep efficiency [16–18], decreased stage 4 sleep [18], and increased movement time [19, 20]. One study reported no remarkable findings [21].

Panic attacks may occur during sleep at night. Nocturnal panic attacks that occur recurrently have been reported in about 18–45% of patients with panic disorder [21–23]. A study using an ambulatory monitoring system also confirmed that 18% of panic attacks occurred during sleep [24]. Patients usually awake abruptly from sleep with physical symptoms similar to their daytime panic attacks. Patients frequently experiencing nocturnal panic attacks may have a fear of going to bed and eventually develop insomnia [25]. PSG studies showed that the attack episodes usually occur following stage 2 or stage 3 sleep [16]. It has been suggested that the presence of sleep panic attacks may define a subtype of panic disorder. These patients were shown to experience early difficulties with anxiety and have higher co-morbidity with affective and anxiety disorders [26]. It has also been proposed that a nocturnal panic attack is a marker of a more severe panic disorder [27]. However, there is not enough evidence to support either of these points of view.

The mechanisms that result in nocturnal panic attacks are not yet fully clear. Daytime panic attacks have been theorized to develop and be maintained by various psychological and physiological factors, such as hypersensitivity to somatic reactions and bodily sensations, conditioned anxiety responses, catastrophic misinterpretations of the somatic reactions, and anticipation of dangers [28]. Since the psychological or cognitive aspects of panic are presumed to be relatively absent during sleep, nocturnal panic attacks should result more from an endogenous physiological mechanism. Proposed possible triggering mechanisms include changes of autonomic functioning [16, 18] and breathing regulation [29, 30] during sleep. One hypothesis suggests that nocturnal panic results from the combination of CO_2 hypersensitivity and the increase of CO_2 pressure that usually occurs during sleep. To test this hypothesis, a study measured the baseline end-tidal CO_2 level and responses to forced hyperventilation and CO_2 inhalation challenges in patients with nocturnal panic attacks, and those who experienced daytime attacks only. The results did not support this hypothesis, and showed no differences between these two groups in their end-tidal CO_2 levels and the frequencies of panic attacks induced by the procedures [23]. Studies have also examined the role of cognitive factors (i.e. , misappraisal of bodily sensations as threatening) in nocturnal panic attacks. It was shown that fake feedback signals during sleep, when they were believed to indicate unusual changes of arousal levels, led to more incidences of panic attacks than when they were believed to signal expected fluctuations of arousal level during sleep [31, 32]. The results suggest that cognitive

factors may still contribute to nocturnal panic attacks in spite of the minimization of cognitive processes during sleep.

Since patients with panic disorder, in general, are more sensitive to bodily sensations [28], sleep pathologies that lead to arousals and somatic reactions may trigger panic attacks during sleep. Irregular breathing patterns and sleep apnea events have been shown to be increased in patients with panic disorder [30, 33]. These respiratory events may result from an obstruction of the upper airway during sleep or be attributable to altered brainstem sensitivity to CO_2 [30]. Symptoms of sleep apnea, such as shortness of breath, feeling of choking, chest discomfort and autonomic reactions to the apnea, are very similar to the features that characterize panic attacks. These symptoms may possibly provoke the nocturnal panic attacks [34]. It is important to rule out sleep apnea syndrome with PSG when evaluating panic patients with predominantly nocturnal attacks.

Sleep and sleep disturbance in post-traumatic stress disorder

PTSD is defined by clusters of symptoms as the consequence of a profound traumatic event. The symptoms include the re-experiencing of the traumatic event (including nightmares), increased arousal (including insomnia), and avoidance of stimuli associated with the trauma [5]. Survey studies also reported that insomnia, nightmares and anxiety arousal are common sleep symptoms in patients with PTSD [35–37]. The content of the disturbed dreams and associated emotions are usually similar to the experiences of the traumatic event. It has been hypothesized that the memory of the traumatic event, by repeatedly stimulating the hippocampus and amygdala (kindling phenomenon), may be imprinted in the central nervous system and re-experienced in the nightmares [38]. The insomnia may in one way reflect the increased overall arousal, and in another way, result from the fear of sleep due to frequent disturbed dreams. However, the insomnia can be persistent and continue despite the remission of both nightmares as well as hypervigilance after treatment with cognitive behavior therapy for PTSD [39]. This implies that the insomnia may have been precipitated by PTSD originally, and with the development of subsequent sleep-specific pathologies the sleep disturbance may be perpetuated.

PSG studies on chronic PTSD patients have shown inconsistent results. Some studies reported no evidence of disturbances in sleep initiation or maintenance [40–42]; other studies showed decreased sleep efficiency and increased awakening [43, 44]. PTSD nightmares typically occurred during episodes of REM sleep, although some studies reported occurrences in NREM sleep [41, 43, 45–49]. Although no typical pattern of REM sleep abnormality has been consistently reported in chronic PTSD patients, various features in REM sleep have been identified in different studies, including increased eye movements [41, 50], increased phasic muscle activations [51], increased brief arousals [52], and increased awakening with and without dream recall [43]. Furthermore, nocturnal awakenings were found to be higher in PTSD patients with frequent nightmares than in idiopathic nightmare sufferers [53]. Taken together, all of these findings suggest an increased arousal level or decreased arousal threshold during REM sleep in patients with chronic PTSD [43, 54].

Studies also compared the PSG sleep of victims of traumatic events who subsequently developed PTSD with those who did not. Development of PTSD symptoms was found to be associated with a shorter average duration of REM sleep and more periods of REM sleep [55] as well as a higher sympathetic activation during REM sleep as measured by heart rate variability [56]. The authors hypothesized that the development of PTSD is associated with increased arousal and, possibly, elevated noradrenergic activity during REM sleep.The rate of sleep-disordered breathing has also been found to be elevated in patients with PTSD [57]. As in the case of panic disorder, nocturnal symptoms of sleep apnea can be confused with or exacerbate the symptoms associated with disturbed dreaming and anxiety arousals in patients with PTSD. The coexistence of sleep apnea syndrome may complicate the evaluation and management of PTSD.

Sleep and sleep disturbance in obsessive-compulsive disorder

Obsessive-compulsive disorder (OCD) is characterized by the presence of obsessions and compulsions. Obsessions are images, ideas, thoughts or impulses that enter the patient's mind repeatedly and that are recognized as irrational by the patient. Compulsions are repetitive or stereotyped behaviors that are performed in response to a specific obsession to prevent the occurrence of an unlikely event or to prevent discomfort [5].

OCD patients report only limited sleep complaints, most frequently difficulty falling asleep and early morning awakening [15]. They seldom present with sleep disturbances as their primary concern. The findings of PSG sleep, performed in patients with OCD, are inconsistent across studies. An early study showed that the sleep abnormalities in patients with OCD generally resembled those of an age-matched group of depressed patients, with decreased total sleep time, reduced stage 4 sleep and shortened REM latency as the primary features [58]. More recent studies, however, reported no sleep abnormalities except for a decrease in sleep efficiency [59, 60]. It is conceivable that the abnormalities of sleep architecture in the earlier study was related to the co-morbid condition of depression [61].

Sleep and sleep disturbance in social phobia

Social phobia is characterized by phobic anxiety and resulting avoidance of social or performance situations [5]. Generally speaking, it is not unusual for patients with social phobia to complain of sleep difficulties; however, sleep disturbances are usually not the primary complaint of phobic patients. Social phobia can further be classified into two subtypes: generalized/pervasive type and discrete/circumscribed type. Patients with generalized social phobia reported relatively more frequent sleep disturbance, with significantly poorer sleep quality, longer sleep latency, and more severe daytime dysfunction [62]. In addition, 70–80% of patient with social phobia may have co-morbid conditions, such as depression and substance abuse [63]. Social phobia patients with these co-morbid disorders tend to have higher rates of sleep complaints, such as increased sleep latency, sleep fragmentation and nightmares. PSG

study of patients with social phobia has been limited. The one PSG study showed no remarkable findings in patients with social phobia. All measures of sleep architecture were found to be comparable to sleep of control subjects [64].

Sleep in mixed anxiety-depressive disorder

Although anxiety disorders and depression are in general considered to be different diagnoses with different pathogeneses, the coexistence of symptoms of both disorders is very common in clinical patients. Research has shown that the rate of anxiety symptoms in depressive patients is as high as 60% . An epidemiological study in the community also reported that 10% of participants with depression symptoms also reported symptoms of anxiety disorders [65]. According to the DSM-IV, these patients, if not fulfilling the diagnostic criteria of either diagnosis, are classified as mixed anxiety-depressive disorder as a type of anxiety disorder not otherwise specified (NOS) [5]. Whether this condition is a milder form of depressive disorders or a subtype of anxiety disorders is still at issue [66, 67]. It has been well-documented that patients with major depression have some specific manifestations in their PSG sleep, including decreased REM sleep latency, increased REM density in the first REM period, and decreased slow wave sleep. These PSG markers were thought to indicate specific neurochemical abnormalities in depression [68, 69]. The possibility of using the PSG to differentiate anxiety and depressive disorders in patients with mixed symptoms has been examined in some studies. Although GAD patients, similar to depression patients, were shown to have prolonged sleep onset latency and decreased slow wave sleep, they do not usually have shortened REM latency and increased REM density, as shown in patients with depression [11, 12, 70]. Studies showed that patients with symptoms of both anxiety and depression had sleep architecture similar to GAD patients, and were differentiated from patients with depressive disorders [71, 72]. However, there are also studies reporting sleep architecture in OCD as similar to those in depression patients, although this may be attributable to the co-morbid condition of depression [58, 61].

Treatment of sleep disturbance in anxiety disorders

As mentioned previously, the causal connection between sleep difficulties and anxiety disorders are often impossible to determine in the clinical domain. The evaluation and treatment of sleep-specific pathologies may be as important as the evaluation and treatment of the anxiety disorders in these cases. Since hyperarousal is a common factor associated with both anxiety and sleep disturbances, the treatments for sleep problems are often similar to those targeting the reduction of worry, tension, and other manifestations of anxiety [73, 74]. However, treatments have also been developed to target specific aspects of certain anxiety disorders or sleep pathologies.

Here we review the pharmacological as well as the non-pharmacological treatments frequently used for the treatment of sleep disturbance in patients with anxiety disorders. The two aspects of treatment may be applied alone or administered in combination to generate better effects.

Treatments of sleep disturbance in generalized anxiety disorder

Benzodiazepines (BZDs) are in general the most common choice of treatments for GAD. Tricyclic antidepressants (TCAs), buspirone, selective serotonin receptor inhibitor (SSRI) and norepinephrine reuptake inhibitors (SNRI), such as venlafaxine, are also considered effective for the treatment of GAD. Although BZDs may have relatively fewer adverse effects and greater tolerability, well-controlled studies of BZDs as a treatment of GAD are limited [75, 76]. In addition, the risks of BZD dependence, withdrawal reaction, memory and psychomotor impairment after long-term usage remain a concern [77]. Imipramine has been shown to be effective for GAD in placebo-controlled studies [78, 79], with therapeutic value equal to BZDs [78, 80, 81]. However, imipramine's various adverse effects, particularly the sedative effect, prevent it from being well accepted. Nevertheless, the sedative 'side effect' can be beneficial for patients of GAD with sleep complaints. Buspirone showed better efficacy than placebo in a therapeutic trial for GAD patients with depression [82]; although its effects on associated sleep complaints were not documented. Some SSRIs, such as clomipramine [83] and paroxetine [79], were found to be effective in the treatment of several types of anxiety disorders. However, paroxetine does not improve the sleep complaints in GAD. Venlafaxine was also shown to be an effective treatment for GAD [84, 85]; however, sleep disruption may result and, therefore, it is not suitable for GAD with sleep complaints [86]. Anticonvulsants, such as valproate and carbamazepine, have also been used in the treatment of GAD; however, their efficacy has not been proven. Serotonin modulators, such as trazodone and nefazodone, have been shown to be effective for GAD in several studies. Trazodone was found to be effective in a placebo-controlled study [78], and nefazodone was shown to be effective in an open trial [87]. Due to their sedative properties, these serotonin modulators and imipramine seem to be a better choice for the treatment of GAD with sleep complaints. Recently, a new line of γ-aminobutyric acid (GABA)-related medications have been shown to be effective in the treatment of GAD. For example, Tiagabine [88], a selective GABA re-uptake inhibitor, and pregabalin [89, 90], a lipophilic GABA analogue, were shown to be effective for the treatment of GAD, These medications await further study.

Cognitive behavioral therapy (CBT) has also been shown to be highly effective in the treatment of GAD [91]. CBT for GAD usually consists of cognitive strategies that target the patients' beliefs or thought processes that are associated with worries, and behavioral practices, which assist the patients to reduce anxiety. One recent study reported that CBT for GAD showed specific effects on patient's insomnia symptoms [92].

Treatment of sleep disturbance in panic disorder

Patients with panic disorder have usually been treated with TCAs [93], monoamine oxidase inhibitors (MAOIs) [94], and high-potency BZDs (i.e. , alprazolam, clonazepam) [95, 96]. Although the MAOIs had demonstrated effectiveness for panic disorder in several studies, they left the sleep complaint relatively unaffected [97].

Treatments with BZDs are effective for daytime panic disorder without sleep disturbance. Alprazolam, for example, was shown to be effective for panic disorder, although withdrawal insomnia secondary to its short half-life was sometimes problematic. Patients may have less of a withdrawal reaction to clonazepam, but panic symptoms may not respond as well to this medication. The effective dosage of BZDs may gradually increase over time. The risk for tolerance and dependence should be considered in long-term use [98, 99]. Recently, several large placebo-controlled trials demonstrated the efficacy of SSRIs, such as fluoxetine [100], paroxetine [101, 102], sertraline [103] and citalopram [104, 105], in the treatment of panic disorder. However, many of these SSRIs lead to the adverse effect of sleep disturbance [106–110]. Trazodone, on the other hand, may be beneficial for sleep complaints; however, it is not effective for the treatment of panic disorder [111]. Elevation of brain α 2-adrenoceptor sensitivity has been reported in panic disorder patients [112]. Central active α 2-adrenergic agonists, such as clonidine, were shown to be effective, but only in short-term use [113]. TCAs have been reported to be effective in both the reduction of overall panic symptoms and the frequency of panic attacks during sleep [93]. Nocturnal panic has also been shown in a case study to respond to anticonvulsants such as carbamazepine [114]. More studies are needed to confirm the effectiveness of anticonvulsants.

CBT is an effective treatment for panic disorder, and has shown long-term efficacy [115]. CBT for panic disorder usually aims at preventing panic attacks and avoidance behaviors. However, there is a lack of data on the effect of CBT on nocturnal panic attacks. Sleep hygiene education and other CBT to reduce sleep-related worries and anxiety can be applied to avoid elevation of anxiety associated with sleep and to avoid maladaptive sleep-related behaviors that may further exacerbate sleep problems.

Treatment of sleep disturbance in post-traumatic stress disorder

Many studies have shown that patients with PTSD respond to TCAs, MAOIs, mood stabilizers, and BZDs to various degrees. The MAOIs have been considered particularly efficacious. TCAs also generated good results. However, the side effects of these agents, particularly the TCAs and the MAOIs, limit their use. As far as the treatment of the core symptoms of PTSD, the SSRIs have been considered to be very effective and have fewer side effects. However, some SSRIs have adverse effects on sleep [116–121]. Although improvement of sleep disturbance has been reported with paroxetine use [116], a study with overnight PSG demonstrated abnormal sleep architecture with frequent sleep fragmentation despite the subjective report of improved sleep quality [122]. Serotonin modulators, such as trazodone [123] and nefazodone [124–126], have also been found to be effective for PTSD and associated sleep complaints. Nefazodone, in particular, was shown to improve the core symptoms of intrusive recollections of the traumatic event, avoidance/numbing and hyperarousal [127] as well as to reduce sleep complaints [124]. Nevertheless, objective assessment of sleep with PSG did not confirm the sleep improvement [124]. Adjunctive olanzapine treatment for SSRI-resistant combat-related PTSD was also reported to be effective in a double-blind, placebo-controlled study [128]. α 1-adrenergic activ-

ity is known to be associated with fear and startle responses. The α 1-adrernergic agonists, such as clonidine [129] and prazosin [130], were also reported as effective for PTSD. In addition, gabapentin, an anticonvulsant, has also been reported to be effective for the core symptoms and sleep complaints of PTSD [131].

CBT plays an important role in successful treatment of PTSD, either as a primary or adjunctive treatment with medications [132]. CBT for PTSD usually comprises a combination of anxiety management, exposure, and cognitive restructuring. Furthermore, the focus of CBT on the management of nightmares and insomnia, including imagery rehearsal, sleep hygiene, stimulus control, and sleep restriction, have been shown to be beneficial for the sleep and other symptoms of PTSD [133–135].

Treatment of sleep disturbance in obsessive-compulsive disorder

Clinical experience suggests that the successful treatment of the core symptoms of OCD can improve the sleep disturbance [136]. Because the sleep complaint in OCD is frequently correlated with co-morbid depression, treatment of the depression is important in these cases. Pathophysiological studies have demonstrated a close relationship between OCD and abnormalities in the serotonergic neurotransmitter system [137]. Most effective treatments of OCD are medicines modulating the serotonergic neurotransmitter system, such as citalopram [138], clomipramine [139], fluoxetine [140], and fluvoxamine [136]. Serotonergic agents with sedating properties, such as clomipramine [139], seem better at addressing the insomnia compared to activating agents, such as fluoxetine [140] and fluvoxamine [136]. In addition, TCAs with both anxiolytic and hypnotic effects, such as trimipramine, are also options for the treatment of OCD with sleep complaints [141]. Antipsychotic medications, such as risperidone, have also been shown to be effective in augmenting the pharmacological response in refractory cases of OCD [142].

Behavioral treatments based on the principles of exposure and response prevention were found to be effective in treating OCD. It has been estimated that more than half of the patients receiving behavioral therapy achieved very good treatment outcomes, and 40% obtained moderate improvements [143]. Long-term follow-up further showed that more than 75% of the patients maintained the improvement with behavioral treatment [143, 144]. In addition to the utilization of exposure and response prevention to reduce the compulsive rituals, other CBTs such as habituation procedures and cognitive restructuring have also been shown to be helpful with obsessive thoughts [145, 146].

Treatment of sleep disturbance in social phobia

Several placebo-controlled studies have demonstrated the effectiveness of SSRIs in the treatment of social phobia, particularly paroxetine [147–150]. However, due to its adverse impact on sleep, the SSRIs may not be the first choice for social phobia with sleep complaints. Serotonin/norepinephrine re-uptake inhibitors (SNRI), such as venlafaxine [151], have also been reported to be effective for social phobia in several open label studies. However, no placebo-controlled trial has been conducted

to confirm this result. Furthermore, as with the SSRIs, the adverse effect on sleep may limit the use of SNRIs for patients with sleep complaints. A recent study examined the effects of gabapentin, an anticonvulsant, in the treatment of social phobia with a randomized, double-blind, placebo-controlled trial [152]. Gabapentin significantly improved symptoms of social phobia. Gabapentin is also known to have beneficial effects in the treatment of sleep disturbance [153, 154]. This medication may be a reasonable choice for the management of sleep disturbance in patients with social phobia.

CBT for social phobia, especially in group therapy format, has been shown to be highly effective [155]. The treatment usually consists of exposure-based techniques and cognitive restructuring. Since the excessive fear of negative evaluation is the central feature of social phobia, a reduction in the degree of concern over the opinion of others was found to be the most important mediating component [156, 157].

As described above, even though the sleep disturbances may develop secondary to the anxiety disorder, sleep-specific pathologies often emerge later and may exacerbate the condition. Sleep hygiene education is recommended for anxiety disorder patients with sleep complaints. Several CBTs for insomnia may also be helpful for the management of the sleep complaints in these patients. Commonly used techniques include stimulus control instructions that eliminate the maladaptive association between bedtime cues and anxiety, sleep-restriction therapy that enhances central sleep mechanisms by systematically curtailing the amount of time in bed, relaxation techniques that promote sleep by reducing physiological tension and cognitive arousal, and cognitive therapies that facilitate sleep onset by alleviating pre-sleep cognitive arousal [158]. Proper management of sleep complaints in anxiety disorders is a reasonable plan. One study showed that individual CBT comprised of sleep hygiene education, stimulus control, and relaxation exercises significantly improved sleep quality in elderly patients with insomnia associated with anxiety disorders, depression, or medical conditions [159]. Furthermore, CBT focused on the management of nightmares and insomnia in PTSD patients have been shown to be effective for both sleep problems and the symptoms of PTSD, anxiety, and depression [133–135].In conclusion, sleep disturbance is an important aspect of anxiety disorders that may play different roles in different disorders. Sleep disturbances may be a risk factor, a core symptom, an associated feature, a triggering factor, or an exacerbating factor for anxiety disorders, or may reflect a primary sleep disorder that shares common etiologies with anxiety disorders. The studies of sleep in patients with anxiety disorders are still limited. Sleep complaints were found in most types of anxiety disorders, although not always consistently reported in PSG studies (see Tabs 1 and 2). Sleep disturbance in some of the anxiety disorders, such as in PTSD, may be associated with the development of underlying pathologies, and may be used to guide treatments. The well-documented PSG features of depression, characterized by shortened REM latency, were not found in the sleep of most of the anxiety disorders. This indicates the differentiation of the pathological mechanisms of depression and anxiety disorders. Studies on the co-morbidity of anxiety disorders and primary sleep disorders, such as sleep apnea syndrome and periodic limb movement disorder, are still very

Table 1. Sleep complaints in anxiety disorders

Types of anxiety disorders	Sleep complaints			
	Difficulty in initiation of sleep	Difficulty in maintenance of sleep	Early morning awakening	Nightmares
Generalized anxiety disorder	++	++	+	+
Panic disorder	+	+	–	+
Post-traumatic stress disorder	++	++	–	++
Obsessive-compulsive disorder	+	–	+	–
Social phobia	+	+	–	+

–: no complaint reported; ++: consistently reported in most studies; +: reported in some studies

Table 2. Characteristics of PSG sleep in anxiety disorders

Types of anxiety disorders	Characteristics of PSG sleep						
	SOL	SE	TST	REML	SWS%	MT	SA
Generalized anxiety disorder	↑↑	↓↓	↓↓	–	↓	–	–
Panic disorder	↑	↓↓	↓	–	↓	↑	↑
Post-traumatic stress disorder	?	↓	↓	–	–	↑	↑
Obsessive-compulsive disorder	–	↓	↓	↓	↓	–	–
Social phobia	–	–	–	–	–	–	–

SOL, sleep onset latency; SE, sleep efficiency; TST, total sleep time; REML, REM sleep latency; SWS%, percentage of slow wave sleep; MT, movement time; SA, sleep apnea events; –, no significant differences; ↑↑ or ↓↓, consistently found increased or decreased; ↓ or ↑, some evidence of increase or decrease; ?, inconsistent results.

limited. This area needs more exploration. Further studies on the sleep disturbance in anxiety disorders will enhance our understanding of the underlying mechanisms and etiologies associated with various anxiety disorders. Systematic understanding will likely help with the evaluation and treatments of both sleep and anxiety disorders. Effective treatment of the core symptoms of the anxiety disorders does not guarantee a corresponding improvement in the associated sleep disturbance. Evaluation and treatment of factors contributing to both the anxiety and the sleep symptoms are often necessary to generate successful treatment outcomes.

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Rebound and withdrawal with benzodiazepine and non-benzodiazepine hypnotic medication

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Introduction

A range of medications is available to treat insomnia, ranging from herbal preparations such as valerian to the recently introduced "z" compounds, zopiclone, zolpidem and zaleplon. Many drugs used for other primary purposes have sedative and sleep-inducing properties as side effects; these include many tricyclic antidepressants and antihistamines.

Insomnia is a common symptom that is difficult to assess. The most common complaint is of insufficient and unsatisfying sleep. However, patients may feel tired during the day, and then blame insufficient sleep without convincing evidence. They then resort too easily to chemical remedies for their putative problem, in the form of self-administered or prescribed medication [1].

Hypnotic drugs, to a greater or lesser extent, are associated with a wide range of unwanted side effects. Those include residual effects the next day [2], and interactions with other drugs [3] and alcohol.

As well as unwanted effects related to direct drug effects, hypnotics, like many other medications, are associated with "offset" effects, namely withdrawal reactions after discontinuation, abrupt or gradual [4]. Numerous terms are used in this context, and include those relating to non-medical use, i.e., abuse and addiction. The purpose of this chapter is to review briefly the clinical problems that can be encountered when discontinuing hypnotic drugs within the normal therapeutic context. For a review on the abuse and dependence potential of the non-benzodiazepine hypnotics, zolpidem and zopiclone, reference should be made to the paper by Hajak et al. [5].

Definition of terms

Cessation of a hypnotic treatment can be followed by several different reactions. The commonest is rebound, which is a worsening of insomnia beyond pre-treatment levels on attempted drug withdrawal [6]. As many patients may have been maintained on hypnotic medication for months or years, the pre-treatment measures of sleep

disturbance may be poorly recollected: rebound may then have to be related to any sleep dysfunction immediately prior to discontinuation.

Rebound may be contrasted with a withdrawal reaction in which stopping the hypnotic is followed by the emergence of new symptoms, not previously experienced by the patient. Muscle tension and pain, loss of appetite and weight, and perceptual changes such as hyperacusis are cardinal features of withdrawal reactions from benzodiazepine-type depressants.

Rebound and withdrawal should also be distinguished from relapse. Rebound is usually self-limiting, whereas relapse continues. However, the relapse does not encompass newly emergent withdrawal type symptoms. Rebound and withdrawal reactions from hypnotics can occur even when no tolerance with escalation of dosage has supervened.

Methodology

As with other aspects of sleep studies, polysomnography (PSG) can provide an exact quantification of rebound in terms of both sleep stages and more sophisticated analyses [7]. However, it cannot measure the clinical implications of the rebound, for example, does the patient feel compelled to resume medication? Nor does it assess withdrawal reactions, except in as much as they often subsume rebound sleep phenomena.

Methods of assessing rebound and withdrawal in more clinically relevant terms have been available for many years (e.g., [8]). In the past decade, regulatory authorities have insisted on discontinuation studies after short-term use as well as long-term maintenance or relapse prevention. This applies to hypnotics in equal force despite most product licences now restricting hypnotic use to short-term (2–4 weeks) use. An adequate number of subjects, normal and insomniac, must be studied. Rebound needs assessment over more than one night, with a variety of techniques including PSG, activity meters, and subjective reports. Standard sleep questionnaires can be used for the subjective assessments.

Withdrawal reactions are more problematical. Hypnotics, by and large, are benzodiazepine like in their pharmacology, receptor binding, etc. The main differences relate to duration of action and to putative selectivity of binding. The benzodiazepine withdrawal reaction has been described many times, and rating scales have been developed to measure the symptoms. Withdrawal reactions from hypnotics would be expected to display similar symptomatic patterns and to follow time-courses dictated by the pharmacokinetic properties of the drug.

One methodological problem concerns long-term use. Withdrawal reactions may not become a possibility until the patient has been taking the medication under review for several weeks or even months. It would be unethical to keep all patients in the study on a potentially dependence-inducing drug for several weeks. Accordingly, patients who have "escaped" close supervision and have extended their use beyond short-term licensing restriction may need to be found. They then become a selected population, but the factors leading to that selection may often be obscure. An alternative is to use

case reports but various biases are then introduced. Thus, the pattern of withdrawal reactions may become apparent but not the incidence or the severity.

Benzodiazepines

Many benzodiazepines have been introduced over the past 35 years as hypnotic medications. The early ones, such as nitrazepam and flurazepam, were long acting (Tab. 1). Indeed, they were so long acting that residual effects were inevitable the next day, and substantial accumulation could occur, especially in the elderly. The next generation of benzodiazepines included the medium acting compounds, such as temazepam, lormetazepam, and loprazolam. Short-acting benzodiazepines were brotizolam and the extensively studied triazolam.

As well as compounds specifically indicated for the short-term treatment of insomnia, some benzodiazepines used primarily as anxiolytics have found extensive usage as symptomatic remedies for insomnia in anxious individuals. Examples include oxazepam, lorazepam, and diazepam. Patterns of use vary from country to country and at different times.

Table 1. Half-lives of some benzodiazepines and similar hypnotics

Benzodiazepine	Elimination half-life (H)
Anxiolytic Hypnotics	
Oxazepam	6–12
Lorazepam	10–20
Diazepam	30–60
Long-acting	
Nitrazepam	25–35
Flunitrazepam	10–20
Flurazepam	40–100
Quazepam	40–100
Intermediate-acting	
Temazepam	10–15
Lormetazepam	10–15
Loprazolam	8–12
Short-acting	
Brotizolam	3–7
Triazolam	3–5
Midazolam	1.5–2.5
Non-benzodiazepine	
Zopiclone	4–6
Zolpidem	2–4
Zaleplon	1–1.5

Most studies relating to rebound and withdrawal with the benzodiazepines were carried out some years ago. They have been reviewed previously [8, 9]. Both healthy individuals and patients with insomnia were used in the studies, which mostly involved the double-blind administration of various benzodiazepines or placebo. The duration of administration could vary between 1 and 28 days. Both PSG and questionnaire data were used, but very few studies have monitored the regular use of benzodiazepine beyond 28 nights. The duration of action and dosage appear to be important factors governing rebound. Long-acting hypnotics such as flurazepam and quazepam showed little evidence of inducing rebound [10, 11]. Occasionally sporadic poor sleep would be found but no consistent results were noted. The somewhat shorter-acting compounds, nitrazepam and flunitrazepam, did produce definite rebound [12–14]. Of the medium-acting hypnotics, temazepam has been most intensely studied, but no consistent rebound has been found (e.g., [8]).

Of all the benzodiazepines, triazolam has been most consistently assessed for rebound potential. Most studies have detected rebound (e.g., [10]). The higher dose of 0.5 mg shows very consistent rebound even after single night administration [15]. Even at the lower and most used dose of 0.25 mg rebound can be found. Other short-acting benzodiazepines, for which rebound has been reported, include brotizolam and midazolam [8, 16, 17]. The severity of rebound was dose related.

Another compound used in some countries as a hypnotic is lorazepam, which can show some rebound phenomena [18]. A similar compound, the chlorinated derivative of temazepam, lormetazepam, shows marked rebound phenomena [19]. Flunitrazepam is a particularly controversial benzodiazepine [20]. It has achieved notoriety as the "date-rape" drug, although documented instances of clandestine use are sparse. It has a high abuse potential, resulting in tight scheduling. However, it does not appear to have a particular propensity to prominent rebound or withdrawal problems.

In summary, therefore, various studies suggest strongly that short-acting benzodiazepine hypnotics are much more likely than intermediate-acting and prolonged-acting hypnotics to induce rebound [21]. Withdrawal studies have been much less consistently pursued but withdrawal potential tends to parallel rebound potential.

Zopiclone

Since 1987 when zopiclone was introduced into clinical practice, extensive evaluations have shown that some rebound changes can be detected in healthy individuals [22–24]. In patients with insomnia more than 20 studies have assessed rebound. Rebound can be found in such patients [25, 26], but is usually more frequent and present in greater intensity in comparison groups given triazolam.

Studies in the elderly have been carefully reviewed by Soldatos and his colleagues [27]. Some deterioration in the soundness of sleep has been detected but the amount of rebound insomnia following zopiclone discontinuation is relatively weak. Although one would certainly expect rebound in a hypnotic with a half-life of around 5 h, the frequency and severity of such rebound seems definitely less than those observed with comparative benzodiazepines such as triazolam and temazepam [28].

Longer-term studies have been designed to detect withdrawal as well as rebound phenomena. A large scale study in France [29] recorded any reactions to stopping zopiclone after it had been taken for up to 12 months. Over a thousand patients took part, most of whom stopped abruptly. In only 1.3 % of the overall population was there substantial evidence of any withdrawal. The symptoms comprised anxiety, irritability, malaise and perceptual changes, which are characteristic of a sedative-type withdrawal reaction. Two parallel studies evaluated the withdrawal following long-term zopiclone and long-term zolpidem [30]. Thirty eight percent of those who withdrew from zopiclone had apparent symptoms, but these were also found in 27 % of those who continued. Most of the withdrawal symptoms related to sleep complaints. Excluding these, no treatment-emergent increase in withdrawal symptoms was found.

An evaluation has been made of the utility of zopiclone substitution in facilitating the withdrawal of flunitrazepam [31]. Twenty-four volunteers with insomnia and a history of long-term benzodiazepine hypnotic use were assessed with both subjective and objective measures during a 5-week substitution with zopiclone and subsequent withdrawal or continuation on flunitrazepam. Withdrawal from flunitrazepam was accompanied a worsening of sleep quality, both subjectively and objectively. No such deterioration was seen in the zopiclone-substituted groups.

Lemoine and Ohayon [32] completed a much larger scale study. Over 1000 patients being treated with a hypnotic were allocated to one of three treatments: gradual substitution with zopiclone; immediate substitution with zopiclone; remained on their benzodiazepine. The gradual and abrupt substitution group had improved sleep during this initial phase; the abrupt substitution group did best. During withdrawal, the last group (benzodiazepine-using) fared worst and more resumed their medication.

The PSG withdrawal effects of zopiclone (7.5 mg), zolpidem (10 mg) and triazolam (0.25 mg) as compared with placebo were studied in 38 healthy subjects over 4 weeks [33]. Slight, non-significant rebound effects on sleep continuity were detected after withdrawal of zopiclone and zolpidem. Total sleep time and sleep efficiency were lower the first night after cessation of triazolam.

A very detailed review of zopiclone noted its proven efficacy and good tolerability [34]. With respect to withdrawal, clinical trials showed no evidence for significant rebound insomnia. The risk of withdrawal reactions was very low, although dependency and abuse have been reported.

Post-marketing surveillance and pharmacovigilance data contain few convincing cases of withdrawal from zopiclone. Most consist of rebound insomnia, but there are a few instances of withdrawal convulsions following high-dose dependence. A review of 25 zopiclone discontinuation studies found rebound effects and withdrawal symptoms to be minimal [35].

Zolpidem

Zolpidem is a very widely prescribed short-acting hypnotic with minimal residual effects [36]. A large portfolio of studies dating back to the early 1990s is extant [37].

The 5-enantiomer of zopiclone, eszopiclone, has recently been successfully introduced into the USA. It is licensed for long-term use. Its rebound and withdrawal potential is presumably similar to that of zopiclone. PSG studies have shown a significant decrease in stage 4 sleep but very little other signs of rebound [38]. These have been reviewed and by and large, rebound and withdrawal following zolpidem (10 mg) is much less than that following withdrawal of an equivalent dose of triazolam, e.g. , 0.25 mg. In the study by Monti et al. [39], total wake time was not significantly prolonged on withdrawal of zolpidem. It can be concluded that there is little evidence for rebound as manifested by sleep recordings after discontinuing treatment with zolpidem (10 mg) [4]. However, higher doses may be associated with some rebound. Subjective measures have also been extensively reviewed [40, 41]. Rebound appears to be minimal.

Some longer-term studies have addressed the question of possible withdrawal [30]. Most putative withdrawal features seen after discontinuation of 10 mg zolpidem were related to insomnia rather than to any newly emergent symptoms. In some older patients, no rebound was detected, and sleep efficacy remained improved over pretreatment baseline [42]. However, a few case reports of withdrawal and dependence have accrued, but are usually noted in patients who have been dependent on another hypnotic or alcohol previously.

Several studies have evaluated the usefulness of zolpidem in facilitating withdrawal from long-term benzodiazepine use (e.g., [43, 44]). It appears that most patients on long-term hypnotics can be transferred to zolpidem and that the subsequent withdrawal from zolpidem is much easier. By and large, such strategies should only be resorted to if simple tapering of the benzodiazepine dosage has proven unsuccessful.

The lack of residual effects, rebound and withdrawal of zolpidem have led to explorations of different regimens of administration. One approach to the deficiencies of long-term nightly usage of hypnotics has been the exploration of the possible efficacy of intermittent use. This can be on a fixed schedule, say every other or third night, or on an "as needed" basis. One study involved 245 individuals with primary insomnia in 58 French primary care centers [45]. Zolpidem was significantly superior to placebo, without any evidence of withdrawal. An even larger study involving 789 insomniacs compared continuous and discontinuous (5 nights/week) administration of zolpidem (10 mg) [46]. Efficacy was slightly but non-significantly reduced in the discontinuous group, but there were no withdrawal problems. Such strategies were both feasible and acceptable [47].

Zaleplon

Zaleplon is the most recently introduced of the non-benzodiazepine hypnotics. No rebound or withdrawal has been reported to any convincing extent.

The ultra short-acting hypnotic, zaleplon was assessed in insomniac outpatients [48]. The doses of zaleplon were 5, 10, and 20 mg and compared to placebo over 4 weeks. Pharmacological tolerance did not develop during treatment with zaleplon, nor were rebound insomnia and withdrawal phenomena apparent.

A review of safety concluded that the use of zaleplon had not been associated with rebound or withdrawal [49]. Another review regarded zaleplon as having an improved risk profile as compared with older compounds [50].

Clinical implications

Despite the widespread and often long-term use of hypnotics, patients are often dissatisfied. A Japanese questionnaire study suggested that 67 % of users were anxious concerning this continued use [51]. Two-thirds of users had decreased their dosage or tried full withdrawal at some time, and more than half had experienced worsening of their condition. Accordingly, compounds that are less likely to be associated with rebound and particularly withdrawal problems are to be welcomed. The recent "z-compounds" are an advance on older drugs, at least as far as these phenomena are concerned. However, some remain unconvinced about the cost-benefits of the newer, more expensive, drugs [52].

Long-term usage of hypnotics is not recommended but is sometimes unavoidable. The newer compounds are regarded as a good option because they do not induce tolerance rapidly and have a low abuse potential [53].

With respect to a specific and common clinical problem, advice to withdraw hypnotic medication should follow a careful evaluation of self-reported sleep patterns, psychological factors and psychosocial status. Ambulant monitoring can be helpful in patients who have encountered severe problems in effecting withdrawal. A careful psychiatric assessment should be made to ascertain whether the patient has clinically significant anxiety and/or depression. Both should be treated with a selective serotonin receptor inhibitor (SSRI) before withdrawal from the hypnotic is attempted. An optimal tapering schedule should be discussed with the patient; some will attempt a rapid withdrawal over less than 8 weeks and others will require much longer. This is particularly so if previous attempts to withdraw have been unsuccessful. Carers, family and friends should be mobilized to help in withdrawal, should the patient wish this. Substitution of zolpidem may facilitate withdrawal but should be kept as a reserve strategy.

Conclusion

The management of insomnia remains inchoate and often neglected by medical practitioners, both generalist and even specialist [54]. The problems with the benzodiazepines became increasingly apparent over the past two to three decades, and yet vast quantities are still being prescribed. The introduction of the safer non-benzodiazepines has led to fewer adverse effects, including rebound and withdrawal. How that translates into clinical safety and acceptability is still unclear. Nevertheless, our therapeutic options have been extended, not only in terms of choice of medication, but also in much more flexible dosage schedules that can be used more successfully in conjunction with non-drug measures [55].

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Sleep disturbances in affective disorders

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Introduction

Sleep disturbances are an integral feature of affective disorders. Episodes of affective illness are often accompanied by marked changes in sleep. Insomnia frequently occurs in mania, and insomnia or hypersomnia often occurs in depression. The observation that sleep deprivation improves mood in about 50–60 % of depressed subjects [1], and that it can even trigger mania in patients with bipolar disorder [2, 3], suggests a close relationship between the regulation of mood and the regulation of sleep. If we assume a neurobiological link between sleep and mood, the recent explosion of basic findings on the functional neuroanatomy of sleep-wake regulation and on the cellular basis of the different sleep rhythms [4–7] should open new ways in our understanding of affective disorders. In the present review, we therefore propose to focus primarily on those findings that enable the integration of sleep-wake electrophysiological and neurobiological data observed in affective disorders with our present knowledge of the sleep-wake mechanisms.

Box 1: Sleep basics

Most sleep researchers recognized three distinct state of existence: wakefulness, rapid eye movement (REM) sleep and non-REM (NREM) sleep. The electrophysiological expression of sleep *versus* wakefulness is attributed to the synchronization and desynchronization of thalamocortical circuits [5, 8]. Clusters of REM, very low levels of muscle tone and wake-like or "desynchronized" (low amplitude and high frequency) EEG activity characterize REM sleep. NREM sleep includes all sleep except REM and is by convention divided in four stages that correspond to increased depth of sleep as indicated by the progressive dominance of "synchronized" EEG activity (i.e. , high amplitude low voltage waves, also known as delta or slow wave activity (SWA); in this respect, sleep stages 3 and 4 are collectively labeled slow wave sleep, SWS). Normal sleep is characterized electrographically as recurrent cycles of NREM and REM sleep of about 90 minutes. In the successive cycles of the

night, the duration of stages 3 and 4 decrease, and the proportion of the cycle occupied by REM sleep tends to increase with REM episodes occurring late in the night having more eye movement bursts than REM episodes occurring early in the night [9].

Sleep EEG findings in affective disorders

Affective illness is a recurrent illness characterized by episodes of depression – and in some cases, mania – that recur and remit repeatedly during the course of a patient's life. A group of minor conditions characterized by chronic intermittent symptomatology such as dysthymia or cyclothymia also exists. Sleep research over the past decades has primarily focused on major affective disorders such as unipolar or bipolar disorders, and minor affective conditions have been neglected in the research literature. Accordingly, the present chapter will largely rely on publication in that field.

Moreover, it is worth noting that most of our knowledge on the relationship between mood and sleep comes from patients with major depression, and for the last decade, from patients with moderate forms of depression. Ethical and safety issues in studying patients with a greater severity of symptoms, especially when patients are unmedicated, could explain the paucity of sleep EEG studies in manic disorder and in severe depression [10].

Depression and antidepressant-responsive conditions

More than 90 % of depressed patients complain about difficulties in falling asleep, sleep disruption, or early morning awakenings [11]. The sleep EEG disturbances associated with major depression have been studied in detail in over 1300 published reports [12]. Well-established objective findings, are disturbed sleep continuity (lengthening of sleep latency and increased wake time after sleep onset resulting in a decreased time spent asleep), deficit of SWS, especially during the first sleep cycle, and REM sleep dysregulation. The latter, also known as an "increased REM sleep pressure" or a "REM sleep disinhibition" is described as a greater amount of REM sleep mostly in the beginning of the night (also reflected by a shortened REM onset latency) and as an increase in actual number of REM during this sleep stage (REM activity) or per minutes of REM sleep (REM density) [13, 14].

Among these different observable sleep EEG disturbances, REM sleep abnormalities were first considered as pathognomonic of major depression [15]. However, many studies in the eighties, and the seminal paper of Benca et al. [16] who meta-analyzed sleep EEG studies performed in different groups of mental disorders, seriously questioned the specificity of this sleep EEG profile for depression. However, Benca et al. [16] mentioned that the most widespread and most severe disturbances are found in patients with depressive disorder. It should also be pointed out that,

beyond depression, shortened REM sleep latencies were more reliably reported in conditions for which antidepressant drugs are now recognized as effective, such as obsessive-compulsive disorder [17], panic disorder [18], generalized anxiety disorder [19] or borderline personality disorder [20]. Polysomnographic recordings in some patients with anorexia nervosa [21] and alcohol dependence [22] could also demonstrate a shortened REM latency, but a depressive comorbidity was clearly present. Accordingly, it may be suggested that the "REM sleep disinhibition" profile provides evidence of antidepressant-responsive conditions rather than of major depression.

Subtypes of major depression

Affective disorders are subtyped according to longitudinal (such as the unipolar-bipolar distinction) or cross-sectional (symptomatological) characteristics. The latter comprises for instance the endogenous/melancholic or psychotic distinction. The question of whether a particular sleep EEG profile could be specific to a subtype of depression was a subject of intense debate in the eighties that has been recently extensively reviewed by Riemann et al. [10]. It was first thought that sleep EEG alteration, and in particular, indications of REM sleep disinhibition, such as a shortened REM latency, could characterize a phenotypic expression of a psychobiological disturbance underlying depression. Attempts to delineate such a subtype remained unsuccessful, the main reason being that numerous confounding factors could affect sleep in depression, such as age, gender, depressive symptom severity, or episode length (see [10], for an overview). Another reason is that depressive subtypes are tightly interrelated, such as the endogenous, the psychotic and the bipolar subtypes [23–25].

Some studies using very large cohorts of depressed patients and multivariate statistics investigated the influence of these different subtypes on sleep EEG parameters, controlling for the effects of confounding factors [26–28]. The design of these studies was to extract from the large sample smaller groups of patients with a subtype and to match them for age and gender to patients without the subtype. Three subtypes were investigated (endogenous, psychotic and bipolar) and between-group differences were further controlled for the effects of symptom severity and of other depressive subtypes. Results show that for most of the sleep EEG parameters the most important influence are those of age (all parameters) and of depression severity (duration of wake after sleep onset, of stage 2 and of REM sleep). After controlling for these effects, the endogenous/non endogenous [26] and the bipolar/unipolar [27] distinctions could not be differentiated, whereas patients with the psychotic subtype had the shortest REM latency [28].

Depression with hypersomnia, bipolar disorder and mania

Some depressed patients, especially if younger, lethargic and/or bipolar, complain of hypersomnia rather than of insomnia [16]. Recurrent winter oversleeping is even considered as a key symptom to diagnose seasonal affective disorder (SAD). Several sleep EEG studies were performed in patients with SAD and none could evidence the typical sleep pattern of major depression (see [10]). Polysomnographic studies

in non-SAD depressed patients with hypersomnia are scarce; one reported a normal nocturnal sleep profile [29] and all studies investigating daytime sleep tendency with the multiple sleep latency test concluded that no signs of objective hypersomnia occurred in this patient group (reviewed in [30]). Therefore, hypersomnia symptoms in depression probably reflect anergia and fatigue rather than true sleepiness. In this regard, in an 24-h sleep EEG study, daytime sleep prevalence of depressed patients was found similar to those of a control group [31].

As previously discussed, nocturnal polysomnographic studies are unable to discriminate bipolar depressed patients from unipolar patients. Only a couple of studies have investigated sleep in unmedicated bipolar manic patients [32–34]. Results suggest that mania is associated with marked disturbances of sleep continuity (delayed sleep onset and reduced sleep period) and of REM measures (shortened REM latency and increased REM density) of a similar nature that has been reported in major depression. Gann et al. [35] also described a rapid cycling patient, with day to day changes from hypomanic to depressed mood, which showed the same abnormalities of REM sleep in the night following a manic day than in the night following a depressed day.

In short, the studies reviewed here indicate that neither typical nocturnal sleep pattern of major depression, nor objective excessive daytime sleepiness could be evidenced in depressed patients with subjective hypersomnia. This suggests that the appearance of objective signs of sleep dysregulation is limited to depressed patients with insomnia complaints. The few studies of manic patients show a same pattern of sleep dysregulation than in insomniac depressed patients.

Trait or state marker?

Other clinicians investigated whether sleep EEG alterations represent episodic ("state" marker) phenomena, can still be detected when the disorder is no longer present ("scar", i.e. , changes in sleep regulation that have been acquired during past episodes), or were already present prior to the clinical onset of the disorder and persist throughout the life-span ("trait" or "vulnerability" marker). Sleep continuity disturbances are typically considered as state markers, resolving or normalizing even after non-pharmacological treatment [36–38]. Diminished SWS and indication of REM sleep disinhibition, such as reduced REM sleep latency or increased REM density, tend to persist despite clinical recovery and are associated with an increased liability to relapse and recurrence [39–41]. A recent prospective study investigating the association between EEG sleep measure and long-term (2–4 years) course of depression further corroborate the idea that sleep continuity disturbances are state markers and that reduced SWS and increased REM sleep pressure are persistent markers [42].

The view that these latter alterations are real "trait markers" rather than "scars" was first suggested by studies showing that cholinergic stimulation during sleep with arecoline provoked, compared to healthy subjects, faster induction of REM sleep in remitted depressives [43] and in euthymic relatives of probands with an affective illness [44]. In addition, some studies demonstrated an increased risk of affective disorders in relatives of depressed patients with shortened REM latencies, compared

to those with normal REM latencies [45, 46]. Moreover, in families of unipolar depressed probands, short REM latency and SWS deficit was shown to characterize affected as well as non-affected relatives of depressed probands with short REM latency [47]. These findings led the authors to propose that sleep dysregulation may precede the clinical expression of the affective illness and constitute therefore a true "trait marker" of the disorder.

Studies of high-risk probands (subjects who have no lifetime or current diagnosis of a psychiatric disorder but who, owing to their family history, are at high risk of development of one) bring further support to this assumption. Schreiber et al. [48], reported that, compared to healthy subjects, subjects at high risk for affective disorders exhibit faster REM sleep induction after the cholinergic agonist RS-86. The same group showed that subjects at high risk for affective disorders displayed a reduced amount of SWS and an increased REM density in the first sleep cycle; furthermore 18 % had an overall sleep pattern that was similar to that of depressed patients [49], independent of the diagnosis (bipolar *versus* unipolar) of their affected relatives [50]. Long-term prospective studies of high-risk probands are now ongoing to investigate whether these polysomnographic abnormalities represents true trait marker. Preliminary results have been published and indicate that, after an average of 3.5 years of follow up, these polysomnographic abnormalities were stable over time [51]. More recently, Lauer et al. [52]. reported that subjects showing a faster REM sleep induction after cholinergic stimulation at study entry have a higher risk for developing an affective disorder during the follow up period.

To summarize, there is now some consistent evidence that diminished SWS and/or a REM sleep disinhibition profile are important correlates of depressive vulnerability and, as such, could be considered as trait markers of affective disorders. In this regard, and although the aforementioned studies need to be replicated, one may already suggest that the cholinergic REM induction test could be considered as an evidence of a cholinergic supersensitivity as a trait or vulnerability marker of affective illness.

Depression and sleep-wake regulation mechanisms

Sleep-wake alternation is governed by homeostatic and circadian factors in complex ways that have been formulated in the two-process model of sleep regulation [53]. Shortly, the propensity to sleep or be awake at any given time is a consequence of a sleep need and its interaction with wake-promoting signals coming from a circadian clock located in the hypothalamus (the suprachiasmatic nucleus, SCN). This wake-promoting signal opposes the sleep need, that progressively increases from morning awakening, ensuring an even degree of alertness throughout the day [54]. At sleep onset, an imbalance between the two opposing influences favor sleep-promoting signals, and the sleep need and its electrophysiological signature, SWA, is at its higher level. Throughout sleep and up to final morning awakening, there is a progressive decline of SWA reflected by the increase of REM sleep proportion across successive REM/NREM cycles.

During the last decade, research lent support to the idea that three interacting neuronal systems (a wake-promoting system, a NREM-promoting system and a REM-

promoting system) are involved in this complex regulation construct. These three neuronal systems could be implicated in the mechanisms of mood-related sleep dysregulation, and particularly, in major depressive insomnia, since both hyperactive wake-promoting system and hypoactive NREM-promoting system could theoretically lead to sleep continuity disturbances and SWS deficit, while a dysfunctional REM-promoting system could underpin the REM sleep disinhibition phenomena.

Disturbances of the wake-promoting system: the hyperarousal theory of depression

Box 2: Wake-promoting system

The wake-promoting or arousal system (of which SCN is only a part of) comprises different structures with widespread cortical projection located in the brainstem, the hypothalamus and the basal forebrain [55]. Monoaminergic transmission is largely implicated in the arousal system; it has been shown that serotoninergic (dorsal raphe nuclei, DRN), noradrenergic (locus coeruleus, LC) and histaminergic (posterior hypothalamus) activity is high during wakefulness, decreases during NREM stages, and becomes almost silent during REM sleep (reviewed in [56]). A group of neurons located in the lateral hypothalamus that produce hypocretin (also known as orexin) seems to play a particularly important role in arousal since it projects not only to over the entire isocortex but to additional arousal systems, including the aforementioned monoaminergic neurons and the cholinergic neurons of the basal forebrain [57, 58].

Indices of an increased activity of wake-promoting mechanisms (or hyperarousal) in major depression come from neuroimaging studies of sleep in depressed patients. In healthy subjects, a robust and significant reduction in cerebral activity is observed in associative cortical areas during NREM sleep relative to wakefulness; NREM sleep is also characterized by reduced metabolic activity in regions promoting arousal such as the mesencephalic brainstem, the thalamus and the basal forebrain (see [59] for a review). Major depression has been characterized, using fluoro-deoxyglucose positron emission tomography (FDG-PET), either by a higher whole brain glucose metabolism [60] or by a smaller NREM cortical (in frontal, parietal and temporal areas) and thalamic deactivation [61]. Given the correlation, observed in depressed patients as in healthy subjects, between relative glucose metabolism and electrophysiological signs of arousal (i.e. , EEG beta activity) [62], a lower NREM deactivation, particularly in thalamic area, supports the hyperarousal theory of depression.

Although a preliminary study showed that hypocretin levels (see Box 2) tended to be higher in depressive than in control subjects [63], there are strong arguments that other mechanisms are involved in the increased wake propensity of depressed patients. Indeed, stress-related responses have been implicated in the neurobiology of depression and striking arguments support the notion that stress may cause brain dysfunctions underlying depression or at least certain features of depression, such

as sleep disruption (reviewed in [64]). Stress-induced arousal responses implicate the corticotropin-releasing hormone (CRH) system and the LC-autonomous nervous (AN) system [65–67]. It has been shown that there is a mutual excitatory influence between the CRH system and the LC-AN system. Such a feed-forward mechanism may be particularly vulnerable to dysfunction during which the arousal reaction is maintained despite the removal of the stressful situation [65, 66]. These authors have proposed that, if prolonged, such dysfunctional arousal state could lead to anxiety and depressive disorder.

Evidence of a stress-related hyperarousal in major depression includes indices of a sustained activation of the CRH system, such as overactivation of the hypothalamic pituitary adrenal (HPA) axis with concomitant inhibition of neurovegetatitive function (e.g. , feeding, sleeping, sexual behavior, reproduction, etc..) [68, 69]. Regarding the LC-AN system, post-mortem studies have shown indication of chronic activation of the LC in patients having committed suicide [70–72] or in depressed patients dying from natural death [73]. Overactivity of the AN system is suggested by studies showing that depression is an important risk factor for adverse cardiovascular events through hyperactivation of the AN system [74, 75]. Another argument for the hyperarousal theory of depression lies on the demonstration that HPA hyperactivity is related to sleep continuity disturbances, SWS deficit, and shortened REM latency, particularly in the most severe subtypes of depression [76–78].

Acute stress has been shown to decrease REM sleep and prolong REM latency [79, 80], a finding in accordance with the well-known inhibitory effect of LC on REM sleep (see Box 4). However, animal studies indicate that chronic rather than acute stress could account for the disinhibition of REM sleep encountered in major depression by the effects of the prolonged activation of the CRH system on serotonin function (reviewed in [64] and [80]). For instance, REM sleep could be indirectly influenced by CRH through its inhibitory effects on dorsal raphe serotoninergic neurons [81, 82] and, more specifically, by the corticosteroid-induced repression of the 5-HT_{1a} receptor gene [83, 84]. Indeed, CNS acting drugs facilitating serotonin transmission at the level of the 5-HT_{1a} post-synaptic receptors have consistently been shown to decrease REM sleep propensity [85, 86].

To summarize, there is now strong evidence that sleep disturbances encountered in major depression are associated with an increase of wake-promoting mechanisms linked to a stress-related hyperarousal reaction implicating the CRH and the LC-AN systems.

Disturbances of the NREM-promoting system: the process S deficiency theory of depression

Box 3: NREM-promoting system

An NREM-promoting system has recently been shown in the ventrolateral preoptic nucleus (VLPO) located in the hypothalamus. Electrophysiological recordings have identified GABAergic SWS-active neurons in this area where lesions produce insomnia in animals and humans [4]. These cells also contain galanin and project to all monoaminergic systems, inhibiting activity during NREM sleep, and receive inputs from multiple brain systems that regulate arousal, autonomic and circadian functions [87]. Recent research implicates adenosine in the homeostatic regulation of sleep via actions on the VLPO and other sleep-regulatory regions [88]. Adenosine functions as a natural sleep-promoting agent accumulating during period of sustained wakefulness and decreasing during sleep; it has been shown to have direct inhibitory effects on arousal systems such as basal forebrain cholinergic neurons and indirect stimulatory effects on the VLPO [89, 90]. Animal studies have shown that increase in extracellular adenosine in cholinergic basal forebrain, either due to sleep deprivation or to microdialysis perfusions of adenosine, increases SWS [88].

In 1982, Borbely and Wirz-Justice [91] suggested that the characteristic sleep disturbances of major depressive patients reflect a homeostatic "Process S" deficiency, i.e. , a failure to accumulate sleep pressure during the daytime that results in a reduced amount of SWS/SWA in NREM sleep, leading to sleep initiation and maintenance difficulties and the early emergence of REM sleep. Most studies, particularly those investigating the first NREM period have shown that, compared to healthy subjects, depressed patients demonstrate lower SWA or decreased delta incidence [91–98], bringing thus support to the "Process S" deficiency theory (see also Fig. 1). Negative findings were from studies which did not restrict their analysis to the first NREM period [99], from studies focusing on high amplitude ($> 75\,\mu V$) delta activity that may not accurately describe changes in amplitude-independent delta across the NREM period, especially in older patients [100, 101], or from small sample studies lacking the statistical power to detect such changes having a large variance [102].

The ubiquitous nucleoside adenosine is a good candidate for the long-sought-for "sleep factor" underlying "Process S". Adenosine both inhibits wake-promoting structures and activates sleep-promoting structure (see Box 3), while its concentrations increase with extended wakefulness and normalize slowly during sleep [103]. The physiology of the adenosinergic transmission has been recently reviewed [104] as well as its implication in sleep-wake mechanisms [88]. Briefly, in humans, adenosine exerts most of its effects through activation of two high-affinity receptors (the A_1 coupled to "inhibitory" Gi proteins and the A_{2A} coupled to "stimulatory" Gs protein). A_1 receptors are involved in the inhibitory effect of adenosine on the cholinergic neurons of the basal forebrain, while A_{2A} receptors are implicated in the disinhibitory effect of adenosine on VLPO neurons. Adenosine, formed by breakdown of ATP, is

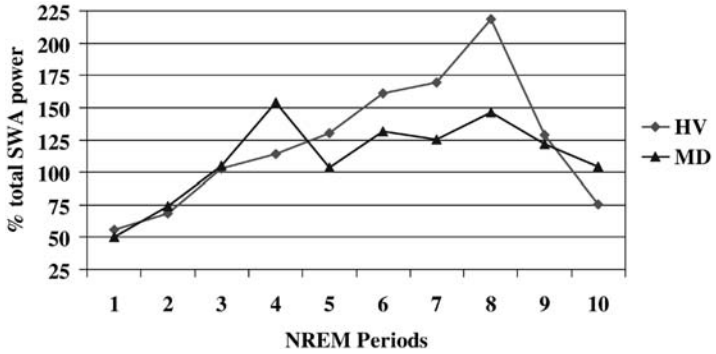

Fig. 1. Time course of slow wave activity (SWA: 0.5–4 Hz) during the first NREM period in 21 major depressed (MD) patients age and gender matched to 21 healthy volunteers (HV) (Period effects: < 0.0001; group effects: NS; Period x Group: < 0.05)

present both intra- and extracellularly, and the balance is maintained by membrane transporters, but when the energy expenditure exceeds energy production, adenosine levels increase in the extracellular space. Thus, the level of adenosine and its modulatory effects are directly linked to the magnitude of the neuronal activity.

In keeping with the S deficiency hypothesis of depression, different manipulations of adenosine transmission in the basal forebrain show that favoring A_1 adenosinergic transmission promotes SWS, while decreasing it, for instance with agents that block A_1 receptors such as caffeine, inhibits SWS and increases wakefulness [88]. However, straight indications of a decrease adenosine transmission in depressive disorders are not found in the literature. A blunted platelet A_{2A} receptor function was described in depressed patients [105], as well as a decreased serum activity of adenosine deaminase [106].

The present section brings some support to the notion that a deficient NREM-promoting system may underlie sleep disturbances in depressive disorder. These arguments are not at variance with those of the preceding section since hypotheses of hyperarousal and of Process S deficiency are not mutually exclusive: both together or separately could explain sleep continuity disturbances and SWS deficit observed in depressive illness.

Disturbances of the REM-promoting system: the aminergic/cholinergic imbalance theory of depression

Box 4: REM-promoting system

The generation of the NREM-REM cycle is explained by a reciprocal interaction model based on anatomical and physiological data and first proposed

by McCarley and Hobson [107] in 1975. This model, that has been regularly revisited (see [56] for the last version) posits a bidirectional inhibitory influence between a REM-promoting system comprising "REM-on" cholinergic neurons located in the laterodorsal (LDT) and the pediculopontine tegmental (PPT) nuclei and both the serotoninergic DRN and the noradrenergic LC "REM-off" neurons. Transition from NREM to REM occurs when activity in the aminergic REM-off neurons ceases. Cholinergic LDT/PPT REM-on neurons are then involved in the initiation of cortical desynchronization through excitatory inputs to the thalamus, and in the occurrence of muscle atonia and rapid eye movements. During REM sleep, the excitatory input from the REM-on neurons to the DRN and the LC leads to a gradual increase in the activity of the REM-off neurons, which in turn inhibit REM-on neurons until the REM episodes ends. GABAergic and glutamatergic modulations of this aminergic-cholinergic interplay have been proposed in the revised version of the model [56].

In line with the reciprocal interaction model (see Box 4), McCarley [108] posited in 1982 that an imbalance between aminergic and cholinergic influences underlie REM sleep disinhibition in depressive disorders. The recent FDG-PET study by Nofzinger et al. [109] studying waking to REM sleep changes brings convincing evidence in favor of the aminergic/cholinergic theory. Compared to healthy subjects, depressed patients showed, during REM sleep, an increased activation of the brainstem reticular formation, the limbic and anterior paralimbic cortex, and the executive cortex. The authors suggested that their findings could reflect the disinhibition of the "REM-on" cholinergic neurons either directly (brainstem activation) or indirectly (through cortical projections).

There are several other arguments in favor of the aminergic/cholinergic imbalance theory. Briefly, in depressed patients, the administration of different cholinergic enhancing drugs (physostigmine, arecoline, RS-86) induced, at various degree, stronger signs of REM sleep disinhibition than in healthy controls, as well as, for some of them, an increased rate of awakenings and arousals [10]. Other convincing arguments come from the monoamine depletion paradigms. Alpha-methyl-para-tyrosine, which inhibits catecholamine synthesis provoked REM sleep abnormalities in humans [110]. Rapid tryptophan depletion induced by a tryptophan-free drink (TFD) also disinhibited REM sleep without changing mood in individuals recovered from depression [111–114]. Bhatti et al. [115] extended these observations to healthy volunteers (in these subjects, TFD decreased REM latency, increased REM expressed as % of total sleep time and increased REM density), findings that were only partially replicated by Voderholzer et al. [116].

We recently investigated whether the administration of a selective serotonin reuptake inhibitor, fluvoxamine, could interfere with the sleep patterns induced after TFD. In this double-blind placebo-controlled cross-over study, 12 healthy male volunteers aged 18–40 years were assigned to two treatment conditions: tryptophan or sham depletion and fluvoxamine or placebo. During each session, separated by a 2-day wash-out period, subjects took either fluvoxamine or placebo and either tryptophan

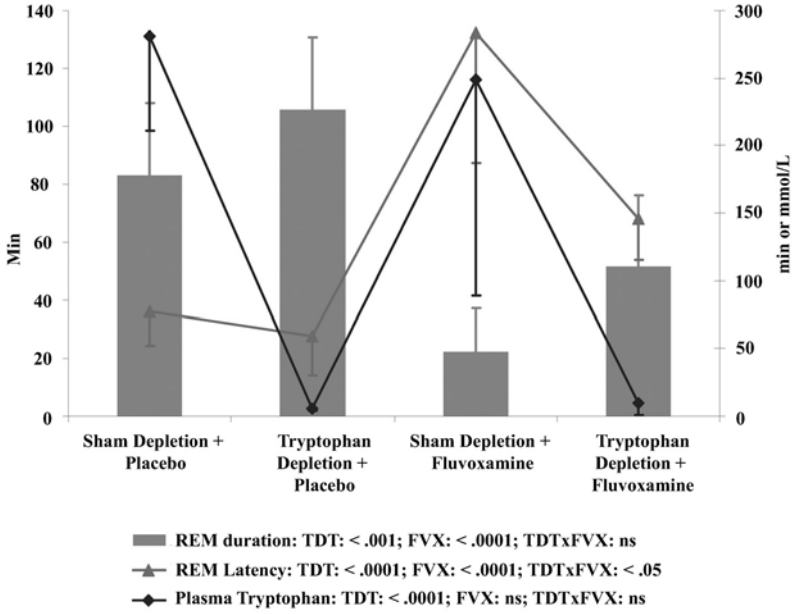

Fig. 2. Effects of a tryptophan *versus* a sham depletion on the REM sleep alterations induced by150 mg fluvoxamine in 12 healthy subjects: a double blind placebo-controlled 4-way cross over study

depletion or sham depletion. Fluvoxamine 50 mg was administered tid, a depletion test was performed at 6 pm and blood was drawn at 11 pm for plasma tryptophan level just before the sleep EEG recordings. Results are summarized on Fig. 2. As it can be seen, they further bring support to the aminergic/cholinergic imbalance hypothesis since both tryptophan depletion and fluvoxamine alter REM sleep, but in an opposite fashion: tryptophan depletion increased REM sleep pressure, whereas fluvoxamine decreased REM sleep pressure. It has to be noted that these effects were more pronounced with fluvoxamine, and that they were only partially balanced with simultaneous tryptophan depletion. Further studies could indicate whether the effects of a lower fluvoxamine dosage would have been completely reversed by the TFD, and if this paradigm could be helpful in dose-finding studies.

Thus, compelling evidence sustains the aminergic/cholinergic imbalance theory. Interestingly, independent of findings on sleep in depression, Janowsky et al. [117] formulated in 1972 their own cholinergic-aminergic imbalance model of affective disorders that postulates a central neurotransmitter disequilibrium with increase cholinergic activity in depression [117]. In the next section we address how this theory, as well as the hyperarousal and the S deficiency theories, fit with experimental data coming from studies investigating the relationship between sleep and responses to antidepressant therapies.

Antidepressive therapies and sleep

The type of research described under this heading aims at correlating therapeutic outcome and pre-therapy sleep as well as therapy-induced sleep alterations. This section is voluntarily limited to the two therapies whose relationships to sleep are the most documented, i.e. , antidepressant drugs and sleep deprivation therapy. The effects of these two therapies are examined in the light of the three theories. According to these theories, effective therapies have either to decrease the arousal level, to increase process S, or to restore the aminergic/cholinergic balance.

Antidepressant drugs

Hyperarousal theory

Decreasing the activity of the CRH or the LC-AN system is theoretically conceivable to lower the arousal level. There is some evidence that antidepressant drugs, including those not directly acting on the noradrenergic system, decrease the activity of the LC in animal models of stress [67, 118] and lower the AN system tone in depressive patients [74, 119]. Preliminary results with the intravenous administration of galanin in depressed patients suggest that this neuropeptide, which decreases LC activity *in vitro* , increases REM latency and has fast antidepressant efficacy [120]. Since CRH elicits its anxiogenic and depressogenic effects through the CRH receptor 1 subtype (CRH-R1) (reviewed in [69]), several CRH-R1 antagonists are currently in development for the treatment of anxiety or depressive disorders. At the present time, one compound, NBI 30775 (also called R121919), has proven efficacious in an open-label phase IIa trial in depressed patients [121]. Interestingly, some of the patients included in the trial underwent polysomnographic recordings, and it was shown that a 4-week treatment with NBI 30775 has a normalizing influence on the sleep EEG by increasing SWS and by decreasing REM density and the number of awakenings [122]. This bring further support to the idea that sleep EEG correlates of hyperarousal in major depression are mediated by overactivity of the CRH system.

S deficiency theory

According to this theory, increasing adenosinergic transmission will restore process S. Only indirect confirmation of this theory is found in the literature on antidepressant drugs. Indeed, human data on the effects of direct adenosine enhancers are lacking since peripheral side effects (hypotension, bradycardia and hypothermia) have so far limited the clinical usefulness of adenosine receptor agonists [104]. However, animal studies have shown that administration of adenosine [123] or of a A_{2A} receptor antagonist [124] produces antidepressant-like effects in models predictive of antidepressant action of drugs in humans. Other evidence is found in studies investigating whether adenosine neurotransmission is affected by effective antidepressant treatments. Thus, tricyclic antidepressants are potent inhibitors of the neuronal uptake of adenosine [125] and potentiate the effects of adenosine [126, 127]. The effects of electroconvulsive therapy and of carbamazepine have also been proposed to be mediated by the adenosinergic transmission (see next section and [128]).

Imbalance theory

This theory is implicitly validated by the fact that most available antidepressant drugs increase monoaminergic transmission and suppress REM sleep. Antidepressant drugs devoid of clear-cut REM suppressant effects (i.e. , amineptine, bupropion, mirtazapine, nefazodone, tianeptine, trazodone and trimipramine) share one characteristic: their potency to inhibit noradrenergic or serotonergic uptake is either absent, doubtful, or moderate (reviewed in [129]). The corollary of the imbalance theory is that REM sleep disinhibition should predict response to antidepressant drugs decreasing REM sleep pressure. In other words indices of REM sleep disinhibition should identify depressed patients responding well to therapies increasing noradrenergic or serotoninergic transmission and poorly to other forms of treatment. To our knowledge, no studies have directly addressed these questions. Indirect evidence supporting this view comes from studies showing that shorter REM latency and increased REM activity identify depressive patients that do not respond to psychotherapy or to placebo [130–132]. Pre-treatment sleep EEG did not have any predictive value on the response rate of bupropion [133] and tianeptine [134], two antidepressant drugs devoid of REM sleep suppressant effect [135, 136]. In contrast, most studies found that a baseline-reduced REM latency has a predictive value on response to tricyclic or serotonin reuptake inhibitor antidepressants [137–141], but there are also two negative reports [130, 142]. Other studies investigated whether REM sleep alteration observed after single administration could predict subsequent clinical response to repeated dosing. Results were inconsistent, some studies being positive [143–145] others not [146–148]. Type and dosage of the antidepressant regimen utilized, as well as duration of treatment, could explain these discrepancies [133, 149].

Sleep deprivation therapy

Hyperarousal theory

Gillin et al. [150] recently reviewed functional brain imaging studies in depressed patients treated with sleep deprivation. Consistent findings across studies were that, before sleep deprivation, responders have elevated metabolism compared to non-responders, in the orbitomedial prefrontal cortex, and especially in the anterior cingulate cortex, a limbic area implicated in affect regulation. Interestingly, an increased activation of the same area (among others) was observed during REM sleep in the study by Nofzinger et al. [109]. However, these findings are not straightforward arguments for the hyperarousal theory since it is postulated that the dysfunctional arousal (or increased activation) is rather diffuse than limited to specific brain area. Regarding the stress-induced arousal responses, there are some indications suggesting that sleep deprivation could induce specific alterations of the CRH and the LC-AN systems. Animal studies have revealed that sleep deprivation decreases the electrical activity of the LC [151]. Moreover sleep deprivation rapidly upregulates several plasticity-related genes, effects that are noradrenergically mediated; these are the very same genes that are upregulated by chronic antidepressants [152]. In healthy subjects, Vgontzas et al. [153] showed that sleep deprivation results in a reduction of cortisol secretion the next day and during the recovery night, and that this reduction

appears to be driven by the increase of SWS and growth hormone (GH) secretion during the recovery night. Based on several observations on the dual and opposite effects of SWS and REM sleep on the somatotrophic system and the corticotropic system, they suggested that reduction of CRH and cortisol may be the mechanism through which sleep deprivation relieves depression. It is noteworthy that Kupfer and Ehlers [154], in a refinement of the S deficiency theory, postulated a disturbance of the interaction of CRH and GH-releasing hormone (GHRH) in the pathophysiology of sleep in depression. They assumed a deficient release of GHRH and an increase output of CRH as playing a key role in depression; therefore in a certain manner, they built a bridge between the hyperarousal theory and the S deficiency theory.

S deficiency theory

The fact that 80 % of responders relapse into depressed mood after the next night of sleep and that a diurnal variation of mood (spontaneous improvement towards the afternoon and evening hours) predicts a positive response to sleep deprivation [155] suggest a role for an antidepressogenic factor accumulating during wakefulness and decreasing during sleep. In a carefully selective REM *versus* NREM sleep deprivation study, it was shown that NREM sleep deprivation was critical to obtain the antidepressant effect; other studies indicate that there are no coupling of REM sleep with the depressogenic effects of naps [10]. This further indicate that the depressogenic factor is related to NREM sleep rather than to REM sleep. Some indirect evidence suggests that adenosine may be implicated. In the basal forebrain of rats, sleep deprivation increased both extracellular adenosine and mRNA of adenosine A_1 receptors, allowing a continued response of the A_1 receptors to adenosine [88]. Since an increased concentration of adenosine in the brain and an associated up-regulation of A_1 receptors are also observed in electroconvulsive therapy (ECT), Berger et al. [128] have proposed that upregulation of A_1 receptors might be instrumental to the antidepressive actions of both sleep deprivation and ECT, and may also be involved in the mechanism of the antidepressive action of carbamazepine, which acts as an A_1 antagonist and thus also upregulate A_1-receptors [156].

Imbalance theory

Many studies suggest that sleep deprivation restores the aminergic/cholinergic balance by increasing the serotoninergic transmission. The effects of sleep deprivation on serotoninergic neurotransmission has been reviewed by Adrien [157]. Briefly, it seems that, at serotoninergic level, sleep deprivation induces the same adaptive changes as those described after chronic treatment with antidepressants. Sleep deprivation in animals enhances the turnover of serotonin, increases the firing rate of serotoninergic neurons in the DRN and downregulates 5-HT_{1A} somatodendritic autoreceptors [157]. In humans, the prolactin response to serotonin stimulation is enhanced after sleep deprivation, and may predict clinical response to sleep deprivation in depressed patients. Moreover, serotonin enhancers may amplify sleep deprivation's efficacy and appear to be related with a functional polymorphism of the serotonin transporter gene (reviewed in [158]). The imbalance theory is further supported by studies in depressed patient showing the predictive value of a baseline

short REM latency, or its prolongation as a clinical response to sleep deprivation (see [10]).

Conclusion

In a previous review on this topic [159], we concluded that only future advances in basic and clinical sleep research could answer whether the various hypotheses proposed to explain REM sleep disinhibition in psychiatric conditions are valid or not, and to what extent they relate to the physiopathology of the illness. About 8 years later, major breakthrough in our understanding of wake-sleep mechanisms brought some responses to this questioning. Most of these response concern major depression, and more specifically patients experiencing insomnia. We discuss here three theories that each could account for only a part of the picture; we assume that they reflect different neurobiological mechanisms operating at various degree in depressed patients. The physiopathology of depression is, of course, very complex and influenced by many factors, such as the genetic background and the context of an adverse environment. It may, however, be conceived that, for many depressed patients, hyperarousal (in response to adversity for instance) is the primary mechanism underlying the sleep disturbances. To act against the effects of hyperarousal on sleep, a constitutional SWS deficit (or S deficiency), such as those encountered in high-risk probands, will be particularly pejorative. Finally, one may speculate that, in susceptible individuals, a prolonged hyperarousal state will lead to an aminergic/cholinergic imbalance and to REM disinhibition. These hypotheses could for instance be tested in longitudinal studies of high-risk probands.

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Clinical Pharmacology of Sleep
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Sleep disturbance in schizophrenia

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Introduction

Psychosis is a syndrome characterized by disordered thinking (delusions, hallucinations, incoherence), and/or severely inappropriate emotions. Psychoses can be categorized either as organic (caused by structural brain defects or physiological dysfunctions) or functional mental disorders; they can be further subclassified as affective or nonaffective. Profound personality disorders, loss of contact with reality and cognitive difficulties result in behavioural disorganization, social withdrawal (by self or reject by others), and psychological malfunction. The most prevalent type of psychoses is schizophrenia, which is found to occur in 0.5–1 % of the general population. Sleep disorders are common in psychoses but, in fact, most of the scientific literature on sleep disorders in psychoses relates to schizophrenia.

Whether sleep disorders is a steady component of the clinical picture of psychoses appears as conflicting. Sleep disorders may indeed be reported either selectively during the acute phase or as a persisting condition in chronically ill patients, stabilized or not by medication. At least some of the discrepancies in the literature appears to stem from the source of information, i.e. , the patient or the polysomnogram [1]. In that respect, the issue of sleep disorder diagnosis in psychoses faces the same dilemma as in insomnia (see chapters 1–4). Indeed, on one hand, one can consider the patient complaining of poor sleep to be always right even though no objective signs are found upon a laboratory recording; the clinician has then to focus on the complaint and unveil what true message it conveys. On the other hand, there is no point in trying to treat a complaint of sleep disorder if no clinically relevant findings can be challenged, no outcome measures to be tested. Without any doubt, discrepancies in the literature on sleep and schizophrenia are also caused by poorly defined clinical variables such as treatment status (primary, adjunctive and previous trials, substance abuse), co-morbidity, age at onset and duration of the disease. This chapter reviews the available literature on sleep disorders in psychoses, mainly schizophrenia, while taking into account confounding variables.

Subjective reports and questionnaire studies

Severe difficulties with sleep onset and sleep maintenance as well as increased bad dreams or nightmares are often reported during the prodromal phase of schizophrenia. While not a diagnostic feature, these sleep difficulties point toward a state of psychic and physiological hyperarousability, testifying to the profound changes taking place at every levels. Difficulty in sleeping is one of the most frequently reported signs preceding relapse as reported by patients themselves and relatives [2]. In the case of bipolar disorders, difficulties with sleep can lead straight into sleep deprivation, which is bound to trigger a manic phase, particularly in rapid cyclers [3]. Sleep is also a matter of worry in acutely ill and in chronic patients with schizophrenia. Long latencies to sleep onset, difficulty remaining asleep as well as disturbing dreams are reported to be particularly irritating [4, 5]. Not unlike non-schizophrenic elderly, older persons with schizophrenia are particularly concerned with the need to improve their sleep [6]. It is thus not surprising to find that the beneficial effects of atypical antipsychotics on sleep quality appear to be particularly appealing to older patients based on questionnaire studies [7]. The contribution of neuroleptics to sleep-wake difficulties is discussed in some detail below, but it is important to remember right from the start that treatment withdrawal can have devastating effects, especially in patients already having insomnia during treatment [8].

Another aspect reported by both patients and clinicians is a shift of the sleep schedule toward a very late bedtime during the prodromal phase, a fact that may contribute to nocturnal dyssomnia and daytime somnolence. A questionnaire study in middle-aged outpatients (18 with schizophrenia and 6 patients with schizoaffective disorders) by Hofstetter et al. [9] also revealed an increased proportion of evening types in these chronic patients compared to controls. The authors also found a correlation between the evening chronotype and poor subjective sleep quality. Whether the preference for late evening activities in patients with schizophrenia translates into objectively measured chronobiological measures is still a matter of debate. Indeed, results of laboratory studies are equivocal, and too few to draw any firm conclusions on the chronobiology of psychoses (see below).

Daytime sleepiness is also often reported in persons with schizophrenia, and it can be understood either as a consequence of poor sleep or a sleep phase problem, but, again, published results are very few. Still, the combined evaluation of nigh time sleep and daytime alertness constitutes an undissociable combination when evaluating any type of treatment. Without any doubt, sedation is a common finding with the use of many neuroleptics, all of which interfere with one or more of the central neurotransmitter systems involved in the regulation of vigilance including dopamine/noradrenalin, serotonin, acetylcholine, and histamine. Among the classical neuroleptics, chlorpromazine and thoridazine appear to be more sedative than haloperidol. In the case of atypical neuroleptics, one can summarize the literature with the following order, from the more to the less sedating molecules: clozapine $>$ olanzapine $=$ quetiapine $>$ sertindole $=$ risperidone. Other factors to be considered while evaluating a neuroleptic molecule for its desired or undesired sedative effect include pharmacokinetics data (absorption, distribution, metabolism, and elimination)

and the use of adjunctive treatments, such as anti-parkinsonians, antidepressants, and anxiolytics. Therefore, many molecules can be used to improve nocturnal sleep, but their residual effects on daytime alertness should always be considered.

While sedative neuroleptics can truly induce sedation and daytime "somnolence", clinical experience shows that what can be wrongly interpreted as daytime "sleepiness" could be a consequence of psychomotor slowing or a manifestation of severe negative symptoms, leading one to retire to one's bedroom to achieve social isolation. Beside secondary effects of sedative neuroleptics, true sleepiness could also be a consequence of sleep apnea syndrome, the incidence of which increases with age, also in persons with schizophrenia [10], often together with a sudden gain of weight following a medication change [11].

Laboratory studies of sleep

The questionnaire studies and clinical experience summarized above lead to a question that has to be answered by objective measures: are the sleep-wake difficulties observed in persons with schizophrenia part of the disease or a side-effect of treatments? In addition to testing clinical hypothesis with neurobiological tools, the results of sleep recordings can point toward neurobiological mechanisms underlying the disease. Indeed, sleep is thought to be governed by a multi-leveled set of executive and permissive mechanisms, encompassing chronobiology and the control of the REM-non-REM cycles and involving all the central neurotransmitter systems mentioned above (for a review see [12]).

Laboratory polysomnographic studies in acutely ill, drug-naïve patients and in neuroleptic-withdrawn patients

Sleep in schizophrenia has been studied in the laboratory from the first days of modern polysomnography, in the middle of the last century, because of the seductive intuitively derived equation between thought disorders and the dreaming state. Recording conditions, inclusion/exclusion criteria and comparison groups were, however, far from optimal according to today's standards. Two more recent reports have used statistical meta-analysis techniques and stringent selection criteria to analyze published studies according to rules warranting for a minimum of control over confounding variables. The first meta-analysis [13] reported on only three studies and found increased sleep latency, decreased total sleep time and decreased slow-wave sleep (SWS; stage 3 + stage 4) in groups with schizophrenia compared to controls. Our own, more recent meta-analysis [14] included 20 polysomnographic studies (321 persons with schizophrenia and 331 controls). The group with schizophrenia showed increased sleep latency, decreased total sleep time and decreased sleep efficiency but no differences in SWS. We also found that sleep disorders were more pronounced in patients withdrawn from neuroleptics compared to neuroleptic naïve patients. These results suggest that sleep disorders in schizophrenia are not a direct consequence of neuroleptic use but are an intrinsic feature of the disease.

Literature reviews and introductory paragraphs of research reports often cite as a fact that SWS duration and REM sleep latency are both shortened in schizophrenia. Still, a detailed analysis of the literature shows that the evidence is far from consistent. In the 20 studies reviewed by Chouinard et al. [14], 13 specifically compared SWS in patients with schizophrenia to controls, and only 2 of those (15 %) found a significant difference. When only stage 4 was considered, this proportion doubled (33 %, or 4 of the 12 available studies). It is, thus, possible that more refined measures of sleep such as quantified analysis of EEG slow-wave activity may be more sensitive to group effects regarding SWS. A comparable situation prevails with regards to REM sleep latency: out of the 20 studies reviewed by Chouinard et al. [14] that compared REM sleep latency, 10 (50 %) found a significantly shorter value in the schizophrenia group, while the result was not significant in the 10 others. Again, uncontrolled variables may be responsible for this variability between studies. For example Tandon et al. [15] showed that the duration of the neuroleptic-free period has an impact on REM sleep in schizophrenia. They found that previously treated patients withdrawn for 2–4 weeks had a shorter REM sleep latency (and greater REM sleep duration) in comparison to patients withdrawn for more than 4 weeks. Gender differences could also explain why the present meta-analysis did not reveal any significant results for REM sleep latency. Goldman et al. [16] have found a significant relation between reduced REM sleep latency and poor outcome in females, but not in males. This suggests that male and female patients with schizophrenia have different pathophysiological mechanisms underlying REM sleep latency.

Finally, it has to be noted that statistical meta-analysis methodology has its limits. Meaningful dependent variables often cannot be included as moderator variables due to the fact that not enough studies report on them, including duration of the illness, chronicity, diagnosis subtype, scale symptoms (e.g. , positive and negative symptoms), and subtypes of neuroleptic treatment. Moreover, such variables are often found to be heterogeneous within most of the studies themselves, so that they cannot not be used with meta-analytic methods. Other variables more closely related to sleep itself are often not controlled for, such as the possibility of napping on the day of recording or the inclusion of participants with a co-morbid sleep disorders (such as sleep apnea and sleep-related periodic limb movements). Figure 1 represents a schematized hypnogram demonstrating most of the sleep disorders described in the literature using laboratory recordings of untreated persons with schizophrenia.

In any case, it is a fact that sleep disorders are an intrinsic feature of schizophrenia. Studies in drug-naïve and neuroleptic-withdrawn conditions prove that patients with schizophrenia have sleep disorders that are not necessarily a consequence of neuroleptic treatments, even though it must be remembered that sleep in neuroleptic-withdrawn schizophrenia patients is not comparable to that of drug-naïve patients [14].

Effects of neuroleptics on laboratory sleep measures

Most studies concerning the effects of neuroleptics on sleep using clinically relevant doses have shown statistically significant improvement on measures of sleep

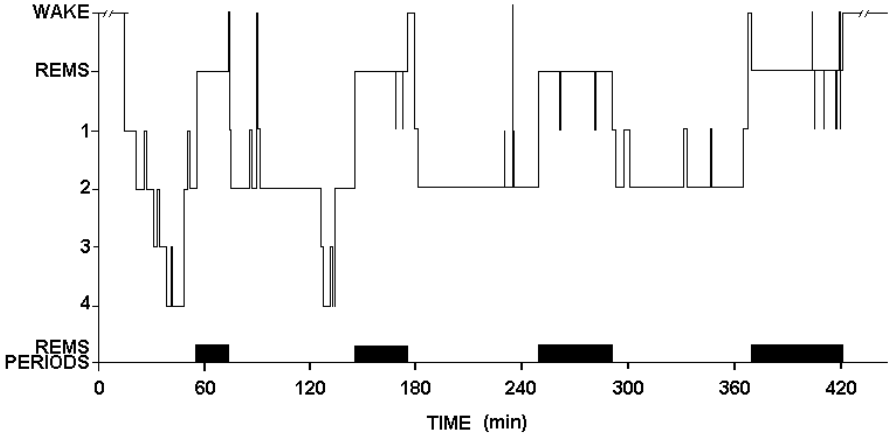

Fig. 1. Schematized hypnogram demonstrating most of the sleep disorders described in the literature using laboratory recordings of untreated persons with schizophrenia. One category of sleep disorders in schizophrenia is the "insomnia type", with long sleep latency, numerous and/or long awakenings, and short sleep duration. Another type of sleep disorders is more concerned with sleep organization, e.g. ., short duration of SWS and/or short latency to the onset of REM sleep. Not all disorders are found in every study since variables such as symptoms or diagnosis subtype, severity and chronicity may influence the results (see text). REMS, REM sleep. A REM sleep period is defined as a succession of REM sleep epochs not interrupted for more than 15 min.

continuity, although not necessarily up to normal values. The effects of neuroleptics on subjective measures of sleep have been described in the previous section and are generally positive besides their sedative side-effects (see above). The reports on sleep architecture using polysomnography are contradictory and depend on the previous treatment-withdrawal regimen and the characteristics of the replacement molecule, not mentioning the fact that double-blind placebo-controlled protocols are disappointingly uncommon in the field. Although neuroleptics undoubtedly have an impact on sleep, studies show that different neuroleptics have different effects on the sleep pattern in patients with schizophrenia. The most recent complete, detailed review on the effects of neuroleptics on sleep in schizophrenia by Monti and Monti [17] shows that typical neuroleptics such as haloperidol, thiothixene, and flupenthixol improve preferentially sleep continuity measures (sleep latency and nocturnal awakenings), while atypical neuroleptics such as olanzapine, risperidone, and clozapine facilitate SWS as well. As mentioned above, neuroleptics interact with most of the central neurotransmitter systems involved in the regulation of vigilance: classical and atypical neuroleptics block dopaminergic, noradrenergic, serotoninergic, cholinergic and histaminergic receptors [18], therefore interacting with variable potency on the control of sleep organization. There is a consensus according to which consolidation of sleep continuity is achieved through dysfacilitation of wake mechanisms via α-adrenergic, histaminergic, and cholinergic receptors antagonists. Irrespective of the issue as to whether or not SWS and REM sleep are normal in schizophrenia,

neuroleptics are thought to facilitate SWS through 5-HT_2 receptor blockade, and the inhibition of REM sleep is probably mediated via D_2 receptor blockade. Noteworthy is the fact that acute melatonin in schizophrenia has been shown to modify sleep in the direction opposite to what should have been expected, with increased signs of insomnia compared to placebo [19].

Conclusions

Sleep disorders are definitively part of the clinical picture in schizophrenia. Due to the lack of space, EEG studies, dream studies and correlative studies have not been reviewed. The evidence is clear that clinical status [20] and daytime cognitive performance [21] covary with sleep in schizophrenia. Future studies should include these issues in their protocol strategies.

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Clinical Pharmacology of Sleep
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Clinical pharmacology of sleep disturbances in children and adolescents

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Introduction

Pediatric sleep medicine and knowledge about pediatric sleep disorders have evolved significantly in the past two decades. However, despite the fact that medications are often used in clinical practice for pediatric sleep disorders, very little empirical data regarding the efficacy, safety, and tolerability of these drugs exist in the pediatric population. This chapter reviews the clinical presentation of the most common pediatric sleep disorders for which pharmacological treatment is used in the clinical setting, including the behavioral insomnias of childhood, parasomnias, narcolepsy, and restless legs syndrome (RLS) and periodic limb movement disorder (PLMD). General consensus-based guidelines for the use of medications for the treatment of pediatric sleep disorders are discussed, as well as the indications for pharmacological treatment in pediatric insomnia, particularly in special populations. Finally, a summary of pharmacological profiles of the most common medications used in pediatric clinical practice specifically for insomnia is presented [1].

Epidemiology of pediatric sleep disorders and medication use

Sleep disorders in children have been identified with unique presenting complaints, although the prevalence rates and natural history of many of these disorders are not well known compared to adult sleep disorders. Epidemiological data from several studies suggest that sleep problems are common in pediatrics; for example, estimates related to difficulty initiating or maintaining sleep range from 25 % in preschool children to 40 % in adolescents [2–6]. Pediatric sleep disorders also have widespread effects with significant short- and long-term consequences on children's health, and on academic, behavioral and social functioning [7–9]. Sleep problems not only affect children, but also their caregivers, with significant impact on family functioning. Furthermore, considerable evidence is emerging that sleep problems may persist or recur in a substantial portion of children [10, 11].

Both prescription and non-prescription medications for pediatric sleep problems are commonly recommended and used by both health care practitioners and parents in the United States and in Europe [1, 12–15]. However, several studies suggest that in clinical practice these medications may not always be used appropriately, or for indications that are warranted [16, 17]. Health care providers are also hampered by the lack of information related to the safety, efficacy and tolerability of various classes of medications. The commonly used medications in various pediatric sleep disorders are discussed below. It is important to emphasize that the majority of these medications have not undergone controlled studies or systematic review to document their efficacy in pediatric sleep disorders. Furthermore, it should be noted that, by and large, these medications are most appropriately used in conjunction with established behavioral sleep strategies [1, 18, 19].

Screening for sleep problems and evaluation of sleep complaints

Lack of screening for sleep problems in the pediatric clinical setting is thought to result in significant under-recognition and under-diagnosis of sleep disorders [1, 20]. Therefore, routine screening for sleep problems is strongly recommended both in the context of well childcare, and as part of the evaluation of any child presenting with behavioral, attention, or learning problems. Several screening tools are currently available, including the "BEARS" [21] and a number of other parent and self-report sleep survey tools [22–24].

Once a potential sleep problem has been identified, a thorough evaluation of the child with a sleep complaint includes a careful history and physical examination. The essential components of the history include a medical and developmental history, assessment of the child's current level of functioning both in school and at home, and the impact of the child's sleep problem on the family. A specific sleep history related to sleep habits, sleep hygiene practices, sleep schedules, and the sleeping environment should be reviewed; sleep diaries are also often helpful in elucidating sleep patterns and behaviors. The sleep history should include the severity, frequency, and duration of the sleep complaint, as well as any attempts at treatment. The need for diagnostic tools such as polysomnography or multiple sleep latency testing is determined by differential diagnosis: in general, polysomnography is reserved for those situations in which sleep disordered breathing or periodic limb movements (PLMs) are suspected on clinical grounds, or there are unusual episodic nocturnal phenomena which may represent partial arousal parasomnias, nocturnal seizures, etc. Referral to a sleep specialist for diagnosis and/or treatment should be considered for children for whom the diagnosis is unclear, for whom behavioral therapy has failed, or in situations in which pharmacological treatment for the sleep disorder is being considered. It should be emphasized that more than one sleep disorder may be present in a given child; e.g. , obstructive sleep apnea and behavioral insomnia. Because the use of medication for one disorder could potentially exacerbate the co-existing sleep problem, the presence of both medically based and behaviorally based sleep disorders must be assessed and appropriately treated.

General medication guidelines

The medication chosen for any child with a sleep disorder should be diagnostically driven, i.e. , determined by the specific sleep diagnosis. Medication should also be viewed in the context of the child's medical history and developmental age, and considered only when appropriately implemented behavioral interventions are not effective. Prior to choosing a pharmacological agent for a targeted sleep symptom such as sleep onset, sleep duration or night wakings, the risks and benefits should be weighed in the context of the clinical situation. Treatment goals which are both realistic and mutually acceptable to the child and family should be determined by the clinician and family, and should be correlated with measurable treatment outcomes. All medications prescribed for sleep problems should be closely monitored for the emergence of side effects. Some medications may also precipitate or exacerbate additional problems such as sleepwalking, confusional arousals, and daytime sleepiness, or may further escalate behavioral problems [25, 26]. Furthermore, discontinuation of these agents may also result in increased sleep problems; for example, increased nightmares may occur if a REM-suppressing medication is withdrawn.

Pediatric insomnia

Much of the information currently available regarding pharmacological treatment for pediatric sleep disorders relates to childhood insomnia [1]. In adults, insomnia is generally defined as difficulty initiating and/or maintaining sleep and/or early morning awakening and/or non-restorative sleep [22]. "Insomnia" is a symptom and not a diagnosis. The definition of insomnia in children is much more challenging because it is often largely parental concerns regarding their child's sleep patterns and behaviors that determine which sleep behaviors are viewed as "problematic". Furthermore, what is defined as insomnia in children has to be considered in the context of normal physical, cognitive, and emotional phenomena that are occurring at different developmental stages. For example, certain sleep behaviors, such as requiring parental presence at sleep onset, may be appropriate in infants, but clearly are problematic in older children.

A recent consensus statement developed by a task force of the American Academy of Sleep Medicine defined pediatric insomnia as difficulty initiating or maintaining sleep that is viewed as a problem by the child or caregiver [1], which may be due to a primary sleep disorder or may be secondary to a co-morbid medical or psychiatric disorder. The 2005 ICSD classification of primary pediatric insomnias (Behavioral Insomnia of Childhood) includes sleep onset association and limit setting types. Sleep onset association type is characterized by "nonadaptive" sleep associations (e.g. , rocking, feeding, parental presence) which the child requires in order to fall asleep at bedtime. During the course of normal nighttime arousals, these children are then unable to recreate this sleep association, requiring parental assistance to return to sleep. The limit setting type primarily involves bedtime resistance; parents typically demonstrate difficulties in adequately enforcing bedtime limits (e.g. , inconsistent or

inappropriate bedtime for the child's age, conceding to multiple requests for attention after bedtime).

Guidelines for treating pediatric insomnia

Even if pharmacological therapy is considered for pediatric insomnia, the importance of sleep hygiene education is critical in any discussion and should be considered paramount in treating children with sleep problems. Behavioral approaches to bedtime struggles and night waking in children have been systematically studied and are the foundation of treatment [18, 19]. Detailed descriptions of behavioral approaches for pediatric insomnia are available [1, 18, 19].

Medication use in pediatric insomnia

First, despite the widespread use of medications for pediatric sleep problems in clinical settings for both normal and developmentally delayed children, there are no medications approved by the Food and Drug Administration (FDA) for the treatment of difficulty initiating and/or maintaining sleep in the pediatric population. The sleep specialist should choose a treatment option that is matched to the patient's clinical situation, and is diagnostically driven rather than aimed at simply resolving the symptom. Examples of indications and contra-indications for use of hypnotics in pediatric insomnia are provided in the consensus statement [1].

Special considerations for pharmacological treatment of pediatric insomnia in children with children with special needs

Sleep disturbances are a common morbidity of psychiatric, neurobehavioral and chronic medical conditions [28, 29]. Not only do children with chronic physical and mental health problems have sleep problems similar to those occurring in normal children, unique factors related to the specific condition (hyperactivity, cognitive delays, pain, etc.) may result in sleep problems which are more severe, more chronic, and more difficult to treat. For example, children with severe neurodevelopmental deficits may be more challenging to actively engage in behavioral management, or may have more difficulty complying with treatments such as continuous positive airway pressure. Regardless of the specific presenting sleep complaint, issues of sleep hygiene in these children, as in normal children, should be actively addressed, and appropriate behavioral management strategies implemented.

A number of children with specific genetic, psychiatric and behavioral syndromes and conditions are susceptible to insomnia. For example, up to 70–80 % of children with autism and pervasive developmental disorder (PDD) [30–33] have sleep problems, including irregular sleep-wake cycles, delayed sleep onset, prolonged night wakings, short sleep duration, and early morning wake times. Sleep problems are

also common in children with blindness (circadian rhythm disorders), Angelman syndrome (disrupted sleep, frequent night awakenings), Williams syndrome (PLMD), Rett syndrome (prolonged sleep onset latency, sleep fragmentation), and Tourette's syndrome (increased nocturnal movements and awakenings) [24, 30]. Children with attention deficit hyperactivity disorder (ADHD) are often reported by parents to have sleep onset difficulties and restless sleep, and present one of the more common chronic conditions for which sedatives are recommended by pediatric practitioners [34–36]. Psychiatric conditions (anxiety disorders or depression) can often present with either insomnia or hypersomnia; 75 % of children and adolescents with major depressive disorder report insomnia, 30 % "severe", and 25 % of depressed adolescents report hypersomnia. Sleep problems may exacerbate the mood and anxiety symptoms; successful treatment of the sleep complaint may improve the psychiatric condition, and vice versa.

Children with other chronic medical conditions, such as asthma [37] or atopy [38] and cystic fibrosis, can be prone to sleep disruption either from medication used to treat the underlying condition, or as a result of poor symptom control. In addition, other factors such as the psychological response to illness, family dynamics, hospitalization-related disruption of normal sleep routines, and related secondary symptoms, such as pain, can significantly impact sleep in these children. Medical conditions which may place children particularly at risk for sleep problems also include severe burns, sickle cell anemia, rheumatological disorders, and chronic headaches.

The approach to insomnia in children with underlying medical or developmental conditions must be viewed in the context of the many challenges of the situation that involves the patient and family. Pharmacological therapy should be considered for sleep problems as part of the overall management strategy, in conjunction with behavioral therapy and sleep hygiene. The American Academy Task Force recommends that sleep problems in these children should be managed aggressively to avoid exacerbation of the underlying condition and improve overall quality of life; longer duration of drug therapy is often necessary in these children [1]. Often, the choices of medications are limited, with significant side effects, and appropriate goals must be set by the clinician and family for improving sleep and quality of life. Consultation with a pediatric sleep specialist is often warranted.

Pharmacological agents for pediatric insomnia

Despite the lack of an ideal pediatric sedative/hypnotic medication, pharmacological agents are widely used for sleep problems in pediatrics. A summary of pharmacological and clinical properties of medications currently most commonly used in the treatment of pediatric insomnia are discussed below (Tables 1 and 2). Although many different classes of medications have sedating properties, only those used in clinical practice for treatment of insomnia are reviewed.

Table 1. Pharmacology of selected medications used for pediatric insomnia [56]

Drug	Class	Mechanism of Action	Half-Life (T ½) (hours)	Metabolism	Onset of Action/Peak Level (min)	Drug-Drug Interactions	Sleep Architecture Effects
clonazepam (Klonopin)	Benzodiazepines (BZD) [57]	Bind to central GABA (gama-aminobutyric acid) receptors	19–60	Hepatic	Rapid absorption; slowed by food 20–60	ETOH/ barbiturates increase CNS de-pression	Supress SWS; reduce frequency of nocturnal arousals
flurazepam (Dalmane)			48–120		20–45		
quazepam (Doral)			48–120		20–45		
temazepam (Restoril)			3–25		45–60		
estazolam (ProSom)			8–24		15–30		
triazolam (Halcion)			8–24		15–30		
chloral hydrate		Unknown; nonspecific CNS depression ?interaction with GABA receptors	10 hr; decreases with increasing age in children; T1/2 infants 3–4x > adults	Hepatic/renal	Onset 30	Increases CNS & respiratory depres-sant effects; may alter effects of anticoagulants	Decreases SOL
clonidine (Catapres)	Alpha agonists	Alpha adrenergic receptor agonists; (guanfacine more selective) decrease NE release	6-24	50-80% of dose excreted unchanged in urine	Rapid absorption; bioavailability 100%; onset action within 1 hr; peak effects 2–4 hrs	Reports of serious CVS effects with co-administration with psychostimulants [58]	Decrease SOL
guanfacine (Tenex)			17				
zolpidem (Ambien)	Pyrimidine derivatives	BZD-like	2–4	Hepatic No active metabolites	30–60	ETOH, CNS depressants may potentiate effects	Decrease SOL, little effects sleep artchitecture
zaleplon (Sonata)			1–2				

Table 1. continued

Drug	Class	Mechanism of Action	Half-Life (T ½) (hours)	Metabolism	Onset of Action/Peak Level (min)	Drug-Drug Interactions	Sleep Architecture Effects
trazadone (Desyrel)	Atypical antidepressant	5HT, serotonin agonist	Biphasic; first T ½ 3–6 hours; second T ½ 5–9 hours 10–36 hours post ingestion	Hepatic	30–120	Potentiates effects ETOH, CNS depressants, digoxin, phenytoin, antihyper-tensives	Decreases SOL, improves sleep continuity, decreases REM, increases SWS
melatonin [59]	Hormone analogue	Main effect circadian; weak hypnotic	30–50 min. Returns to baseline levels in 4–8 hours Biphasic elimination; 3 min and 45 min 90% excreted in 4 hours	Hepatic	30–60 (sustained release peak level 4 hours)	Largely unknown; NSAID's ETOH, Caffeine, BZD's may interfere with normal melatonin production	Decreases SOL; main effect on circadian rhythms
diphenhydramine (Benadryl) brompheniramine chlorpheniramine hydroxyzine (Atarax)	Antihistamines	H1 subtype receptor agonists; 1st generation drugs cross blood-brain barrier	(Duration of action) 4–6 4–6 4–6 6–24	Hepatic	Rapid absorption and onset of action; Peak levels 2–4 hours	ETOH/CNS depressants (barbiturates, opiates)	Decreases SOL; may impair sleep quality

SWS = Slow Wave Sleep (Stage 3-4), SOL = Sleep Onset Latency, BZD = Benzodiazepine, NSAD = Non Steroidal Anti-inflammatory Drug, ETOH = Alcohol

Table 2. Pharmacology of selected medications used for pediatric insomnia [56]

Drug	Adult Dosing Range (mg/d)	Formulation	Side Effects	Development Tolerance/ Withdrawal Effects	Safety Profile/ (Overdose)	Comments
clonazepam flurazepam quazepam temazepam estazolam triazolam	0.5–2.0 15–30 7.5–30 15–30 1–2 0.125–0.25	Tablets	Residual daytime sedation, rebound insomnia on discontinuation, psychomotor/ cognitive impairment, anterograde amnesia (dose dependent); impairment respiratory function	Yes, especially with shorter acting BZD; withdrawal effects include seizures	Marked abuse pontential	Also used to control partial arousal parasomnias (night terrors, sleep-walking); use short half-life BZD for sleep onset; longer half-life for sleep maintenance
chloral hydrate	50–75mg/kg; max 1–2 gm per dose	Capsules, syrup, rectal suppository	Respiratory depression GI (nausea, vomiting, especially if taken w/out food), drowsiness/ dizziness	Yes, withdrawal after prolonged use may cause delerium, seizures	Poor tolerability safety profile; OD: CNS depression, cardiac arrythmias, hypothermia, hypotension	Reports of possible liver toxicity, respiratory depression limit use
clonidine guanfacine	0.025–0.3 (up to 0.8) Increase by 0.05 increments 0.5–2	Tablet, transdermal patch	Dry mouth, bradycardia, hypotension, rebound hypertension on discontinueation		Narrow therapeutic index; OD-bradycardia, decreased consciousness hypotension	Also used in daytime treatment of ADHD
zolpidem zaleplon	5–10 5–10		Headache, retrograde amnesia; few residual next-day effects	May develop tolerance/adaptation with extended use; May develop rebound insomnia on discontinuation	Well-tolerated in adults/OD: CNS depression; hypotension	Little clinical experience in children

Table 2. continued

Drug	Adult Dosing Range (mg/d)	Formulation	Side Effects	Development Tolerance/ Withdrawal Effects	Safety Profile/ (Overdose)	Comments
trazadone	20–50	Tablets	Dizziness, CNS overstimulation. Cardiac arrythmias, hypotension, priapsim		OD: hypotension, cardiac effects	May be used with co-morbid depression
melatonin	2.5–5 (0.3–25)	Tablet; various strengths	Largely unknown; reportd hypotention, bradycardia, nausea, headache Possible exacerbation of co-morbid auotimmune diseases		unknown	Used in children with developmental disabilities, MR, autism, PDD, neurologic impairment, blindness; jet lag
diphenhydramine brompheniramine chlorpheniramine hydroxyzine	25–50 (should not exceed daily dose 300mg) 4 4 25–100; 0.6mg/kg (children)	Tablet, capsule, syrup, injectable	Daytime drowsiness, GI (appetite loss, nausea/vomiting, constipation, dry mouth), paradoxical excitation		OD: hallucinations, seizures, excessive stimulation	Weak sophorifics; high level parental/practioner acceptance

Benzodiazepines

Benzodiazepines activate the GABA receptor and help initiate and maintain non-REM sleep and generation of sleep spindles, but most disrupt slow wave sleep (SWS). In pediatrics, these medications have been used for many years for sedation and as anticonvulsants, less often as hypnotics. The different medications that are in the benzodiazepine class share hypnotic, anxiolytic, muscle relaxant, and anticonvulsant properties. The shorter onset of action of some benzodiazepines is useful for treating sleep onset insomnia. Agents with a longer half-life and duration of action often assist with maintenance of sleep, but may result in morning "hangover", daytime sleepiness, and compromised daytime functioning. There is a risk of habituation or addiction with these medications. This class of medication can be used generally for short-term or transient insomnia, when medication is indicated only for a brief period of time.

Clonidine

Clonidine is one of the most widely used sedating medications in pediatric and child psychiatry practice, particularly in children with sleep onset delay and ADHD. It is a central $alpha_2$ agonist. Pharmacokinetics show rapid absorption, with an onset action within 1 h, peak effects at 2–4 h and a half-life 6–24 h. Effects on sleep architecture are fairly minimal but may include decreased REM, so that discontinuation can lead to REM rebound. Clonidine has a narrow therapeutic index, and there has been a recent dramatic increase in reports of overdose with this medication. Potentially significant side effects including hypotension, bradycardia, anticholinergic effects, irritability, and dysphoria; rebound hypertension may occur on abrupt discontinuation. Tolerance often develops, necessitating increases in dose.

Pyrimidine agents (non-benzodiazepines)

Zaleplon (Sonata) is a non-benzodiazepine medication that binds to the benzodiazepine receptor. It has a very short half-life, making it useful for sleep onset insomnia. Effects on sleep architecture appear minimal, although it may increase SWS. It has been shown to be safe in recent studies [39]. The most common side effect reported in adults is headaches. Use of zaleplon has not been studied in children, except in one study where it was used for sedation purposes. Therefore, its potential role in the clinical treatment of pediatric insomnia is not known.

Zolpidem (Ambien) is also a hypnotic agent that acts at the $GABA_A$ receptor site by binding selective GABA receptors. It can be used for sleep maintenance insomnia or night awakenings because of its slightly longer half-life of 2–3 h. No published efficacy studies in the pediatric population exist; a single case series which described 12 accidental ingestions in a group of children aged 20 months to 5 years and 5 intentional ingestions in 15–16 year olds [40] reported onset of central nervous system (CNS) symptoms but no fatalities.

Tricyclic antidepressants

Tricyclic antidepressants (TCAs) have been used to treat children with mood disorders, as well as with ADHD, for a number of years. Most TCAs are REM sleep suppressants; thus, rapid withdrawal may lead to REM rebound and nightmares. The choice of an antidepressant for a mood disorder with concurrent sleep problems depends on whether there is insomnia or hypersomnia. Treating the underlying mood disorder will often result in improved sleep. Most TCAs are sedating, although they vary in the degree of sedating properties. The most activating TCA is protriptyline, which can be used for the hypersomnolent child; however, it should be avoided in children with sleep onset or sleep maintenance difficulties. The most commonly reported side effects of TCAs are anxiety and agitation, as well as anticholinergic effects; because of their cardiotoxicity, they should be used with extreme caution in clinical situations in which there is a risk of accidental or intentional overdose.

Serotonin antagonists/reuptake inhibitors

Selective serotonin reuptake inhibitors (SSRIs) promote sleep by inhibiting uptake of serotonin. They vary widely in their propensity to cause sleep onset delay and sleep disruption (e.g. , fluoxetine) and sedation (citralopram). Trazadone, a 5HT agonist, is a more powerful sedating agent because it inhibits binding of serotonin and blocks histamine receptors, thus sedating via two mechanisms. SSRIs may exacerbate preexisting RLS and PLMs.

Melatonin

Melatonin is a hormone secreted by the pineal gland in response to darkness, and is controlled by the suprachiasmatic nucleus. Possible clinical uses for melatonin include: circadian rhythm disturbances in normal children and children with special needs (blindness, Rett syndrome) and jet lag. The mechanism of action of commercially available melatonin is to minimize the endogenous pineal hormone. It has mild hypnotic properties and can help with sleep onset by reducing sleep onset latency, but it does not help in maintaining sleep. The plasma levels of exogenous melatonin peak within 1 h of administration. The potential side effects of melatonin include lowering of seizure threshold in some individuals, and potential suppression of the hypothalamic-gonadal axis such that precocious puberty can occur. Melatonin is not regulated by the FDA; therefore, the commercially available formulations vary in strength, and purity. Reported doses for melatonin include: 1 mg in infants, 2.5–3 mg in older children, and 5 mg in adolescents. Use of melatonin in children with special needs have reported doses ranging from 0.5 mg to 10 mg, irrespective of age. One caveat is that melatonin is frequently used for inappropriate indications in clinical settings and can worsen the sleep problems.

Other classes of medications that may be used for pediatric insomnia include mood stabilizers/anticonvulsants (depakote), other classes of antidepressants (mirtazapine), atypical antipsychotics (risperidone), and chloral hydrate, as well as herbal

preparations such as chamomile and valerian root. Newer atypical antipsychotics have weight gain as a significant side effect and can worsen obstructive sleep apnea. With the exception of a handful of clinical trials with herbal medications, which have shown some positive effects on sleep onset, there are no empirical data in children to support efficacy or safety of any of these medications.

Antihistamines
Both prescription and over-the-counter antihistamines are the most commonly prescribed/recommended sedatives in pediatric practice. They bind to H_1 receptors in the CNS, with only the first generation medications crossing the blood-brain barrier. They are generally rapidly absorbed. Effects on sleep architecture are minimal. Side effects include daytime drowsiness, cholinergic effects and paradoxical excitation. In general, these drugs are rather weak soporifics, but parental and provider familiarity tend to make them a more acceptable choice for many families.

Pharmacological treatment for other pediatric sleep disorders

The partial arousal parasomnias, which include sleep walking and sleep terrors, have several features in common. Because they typically occur at the transition out of stage 4 or SWS, partial arousal parasomnias have clinical features of both the awake (ambulation, vocalizations) and the sleeping (high arousal threshold, unresponsiveness to the environment) state, and there is usually amnesia for the events. They are more common in preschoolers and school-aged children because of the relatively higher percentage of SWS in younger children. The typical timing of partial arousal parasomnias during the first 2 h of sleep is related to the predominance of SWS in the first third of the night. Finally, there appears to be a genetic predisposition for both sleepwalking and night terrors. Confusional arousals are parasomnias, which can occur at any age characterized by disorientation, confusion and amnesia. Night terrors are another parasomnia that occurs in about 1–3 % of children and are characterized by intense autonomic arousal and disorientation. Sleepwalking is another commonly encountered parasomnia with a prevalence rate of 1–15 % in the population [25]. The clinical history is often sufficient to make the diagnosis, but overnight polysomnography may be considered when the presentation is atypical or seizures are a part of the differential diagnosis.

Management of parasomnias

The treatment of partial arousal parasomnias generally first involves education for the parents and the patient since many of these parasomnias are benign and self-limited. Safety is the most important consideration because the affected patient is unaware of potential danger. A common sense approach to address safety concerns should be discussed, such as ensuring there is a security system to alert the family of the child's attempt to leave the house. It is imperative to address factors that may increase SWS, and thus exacerbate night terrors including illness, sleep fragmentation and

sleep curtailment. Therefore, it is recommended that the child's sleep be extended and schedule maintained to minimize disruption.

There is clear consensus regarding which pediatric patients with parasomnias require pharmacological treatment; however, the frequency of events (both per night and per week), the severity, and the amount of disruption to the family should be considerations, as well as safety issues. Medications that have been reported to be efficacious in case studies for all classes of parasomnias, include TCAs and benzodiazepines [25]. Although there are no controlled studies, benzodiazepines, particularly clonazepam, have been reported as being effective for night terrors and sleepwalking [25]. In several small case series, behavioral intervention with scheduled awakenings for parasomnias has also been shown to be helpful [41, 42]. Disorders of arousal such as parasomnias are a common problem and can be evaluated and treated by a sleep clinician without the need for long-term pharmacotherapy.

Narcolepsy

Narcolepsy is a lifelong neurological condition with characteristic symptoms including: excessive daytime sleepiness, cataplexy (sudden complete or partial loss of muscle tone triggered by emotion), hypnogogic hallucinations and sleep paralysis [27]. Narcolepsy is associated with sleep/wake dysregulation, particularly involving REM sleep. Associated night-time sleep disruption with frequent awakenings is commonly reported. The prevalence of narcolepsy in children is not known, but overall estimated prevalence in the United States is 3–16 in 10 000 [6, 22]. Most individuals report onset of symptoms during adolescents, although clinical reviews have reported onset of symptoms in children [43, 44]. The associated morbidity caused not only by delayed diagnosis, but the functional impairment from the symptoms of narcolepsy can be significant [45].

The pathophysiology of human narcolepsy is associated with absence of hypocretin-1 in the cerebrospinal fluid [46]. An association has also been found between narcolepsy and the histocompatibility leukocyte antigen (HLA) DR2, specifically DQB1*0602 and DQA1*0102, which are present in 95–100 % of patients with narcolepsy. However, the presence of histocompatibility antigens is not considered diagnostic [47]. Secondary narcolepsy has also been reported, resulting from CNS tumors involving the posterior thalamus, brainstem or third ventricle, and other conditions such as Niemann Pick disease Type C [25]. The diagnosis of narcolepsy is based on history and on the overnight polysomnogram to rule out other sleep disorders in conjunction with a positive multiple sleep latency test (MSLT) [48]. The criteria for diagnosing narcolepsy includes the presence of two sleep onset REM periods during the MSLT following a normal overnight polysomnogram.

Management of narcolepsy

Narcolepsy is a lifelong condition with significant implications for the affected individual. The treatment plan is aimed at controlling symptoms to enable the affected

person to function. Sleep hygiene education should be provided, such that a regular sleep schedule is maintained. Scheduled naps are recommended as part of therapy in conjunction with medications. Behavior modification, such as restricting driving, has to be incorporated into the management plan because of the risk of injury secondary to the sleep attacks or excessive sleepiness. Daytime sleepiness of narcolepsy is treated with stimulants (methylphenidate or amphetamines), which are available in several preparations and doses vary based on the preparation. It should be noted that there have been no systematic studies for use of stimulants or any medications for narcolepsy specifically in children. The following have been used:

- Methylphenidate (Ritalin; Ritalin SR; Concerta; Metadate); doses range from 5 mg/day bid to a maximum of 60 mg/day, divided tid. Side effects include nervousness, insomnia, loss of appetite and headaches.
- Dextroamphetamine (Dexadrine); doses range from 5 to 25 mg/day divided bid.
- Modafinil; another wakefulness promoting agent with an unknown mechanism of action; used for narcolepsy in adults and being studied for use in children at present; dose range is 100–400 mg/day divided bid. Side effects include headaches, anxiety, nausea and nervousness.

Cataplexy requires additional treatment, as stimulants are not effective. Medications for suppressing REM sleep improve other features of narcolepsy, i.e. , use of:

- TCAs: clomipramine: 25–75 mg/day in one to two divided doses
- Imipramine: 25–100 mg/day
- Protriptyline: 2.5–10 mg/day in one to two divided doses
- Sodium oxybate: an endogenous neurotransmitter, recently found to alleviate cataplexy; consolidates sleep and increases stage 3–4 sleep at night. Dose: 3–9 g in two divided doses at night.
- Other antidepressants: fluoxetine: 10–40 mg/day in the morning
- Venlafaxine: 75–150 mg/day in the morning
- Sertraline 25–100 g/day in the morning

Future potential treatments may include hypocretin analogues.

Narcolepsy is a lifelong disorder without a known cure. At present, ideally, the goal is to control the symptoms to enable the affected individual to have a good quality of life. Patients with narcolepsy should be referred to a sleep specialist for evaluation and treatment. Regular retesting is recommended; however, the patient needs to be medication free for a minimum of 2 weeks to facilitate repeat testing.

RLS/PLMD

RLS is a sensorimotor condition which affects primarily the lower extremities, characterized by subjective sensations of discomfort associated with an irresistible urge to move the legs; the sensations are exacerbated during periods of inactivity and are relieved temporarily with movement. In children, these complaints may present as bedtime resistance or refusal to go to sleep because these sensations are worse in

the evenings as the person tries to initiate sleep. A substantial portion of affected adults have reported onset of symptoms of RLS prior to age 10 [49]. RLS is also associated with inattention and hyperactivity [50–53]. Primary RLS is considered idiopathic and a autosomal dominant genetic link has been suggested. Reports of secondary RLS have been described in adults, and can be associated with iron deficiency anemia (specifically low ferritin levels), vitamin B12 or folate deficiency, pregnancy, neurological disorders involving myelopathy or radiculopathy, end-stage renal disease and diabetes. In children, RLS has been found to be more common in Williams syndrome. Recently, criteria adapted for children with RLS have been developed by Walters et al. [54]. The diagnosis of RLS is based solely on clinical history.

Repetitive, stereotypic, serial limb movements that occur during sleep at intervals of 20–40 s characterize PLMD. The diagnostic criteria for PLMs include a series of four or more leg movements, lasting 0.5–5 s in duration and occurring within a 90-s interval. An index of more than five PLM with arousal/hour is considered abnormal in adults, although strict criteria have not been established in children [27]. The majority of the movement is restricted to the lower leg and may or may not be associated with a partial arousal. PLMD can occur concomitantly with RLS. It is estimated that 80 % of individuals with RLS have PLMs. Conversely, individuals with PLMD have a much lower likelihood of having RLS, in the 20 % range.

Dopamine is thought to play a role in the pathophysiology of RLS and PLMD because of the reported improvement in symptoms with dopamine agonists. Secondary causes of PLMD include obstructive sleep apnea, certain medications such as TCAs and SSRIs. Affected individuals with PLMD may present with frequent nighttime arousals or excessive daytime sleepiness, or may be entirely asymptomatic. Similar to RLS, PLMD has also been associated with ADHD in children [50–53]. Patients complaining of symptoms of PLMD with daytime effects should be objectively evaluated to determine the severity of the PLMD with an overnight polysomnogram.

Management of RLS and PLMD

There is an association between iron deficiency anemia and RLS; thus patients should be screened with complete blood count indices and for serum ferritin level. The iron deficit will not be found using normal parameters such as a complete blood count and iron level. A serum ferritin level of <50 is associated with RLS.

Similar to other sleep disorders, non-pharmacological intervention is an important component of therapy (regular exercise, good sleep hygiene) and includes education for avoiding exacerbating factors for RLS and PLMD. The decision for pharmacological intervention should be based on severity of the symptoms, degree of sleep disruption and associated daytime sequalae. For example, even an elevated PLMD index in the absence of arousals or daytime sequalae does not warrant medication. In contrast, for moderate to severe disease or significantly elevated index, the decision to treat is self-evident. Iron supplements should be provided for individuals with low serum ferritin levels. The underlying principle mandating therapy includes

choosing the medication with the least side effects and the lowest dose to control symptoms. The choices of medications are listed below and adult doses are listed. The only data reported in children include the use of levodopa or pergolide in seven children with RLS and PLMD with ADHD [55]. Improvement was reported in all seven children without side effects. The longest period of use in this case series was 3 years. Overall, systematic evaluation of these medications for RLS and PLMD in children are lacking.

Dopamine precursors are considered first-line in adults. Side effects include orthostatic hypotension, insomnia, daytime fatigue, and somnolence; nausea, and augmentation may occur. Levodopa with benserazide or carbidopa (Sinemet): 100–125 mg or 200–250 mg at bedtime and additional doses may be needed. Dopamine agonists are becoming more popular because of the fewer side effects, and less augmentation. These are used to treat RLS and PLMD. Their side effects include nausea, orthostatic hypotension, insomnia, and somnolence; also, the potential for tolerance exists.

Most commonly used medications are:

- Pramipexole (Mirapex) 0.125–1.0 mg at bedtime, and pergolide (Permax) 0.1–0.5 mg at bedtime.
- Benzodiazepines have been used for RLS and PLMD. Caution is advised because this class of medication may worsen obstructive sleep apnea.

Commonly used medications include:

- Clonazepam (Klonopin) 0.5–2.0 mg at bedtime
- Temazepam 15–30 mg at bedtime
- Nitrazepam 5–10 mg at bedtime.

Opiates are used in RLS and PLMD, but because of risk of dependency and habituation, these are not considered first line of treatment. Oxycodone (Percodan) 5 mg at bedtime, or propoxyphene (Darvon, Darvocet) 200 mg at bedtime; or codeine 15–60 mg at bedtime.

Anticonvulsants are used for RLS. Most common side effects include daytime somnolence: carbamazepine (Tegretol) 200–400 mg at bedtime or gabapentin (Neurontin) 100–400 mg at bedtime are often used.

Clonidine is used for RLS; 0.05–0.2 mg at bedtime; the side effects include hypotension.

These medications, although used clinically, have not been evaluated for children.

Conclusions

Pediatric sleep disorders are common, have significant effects on daytime functioning of children and families, and most are amenable to some combination of behavioral management strategies and pharmacological treatment. It is particularly important for the primary care physician to screen for sleep problems in children,

especially in high-risk populations. A detailed history evaluating circumstances related to the sleep problem should be obtained. Addition of pharmacological therapy to non-pharmacological interventions for pediatric sleep disorders for disorders such as insomnia, parasomnias, narcolepsy, RLS or PLMs should be diagnostically driven, and should consider both the best match between the medication type and individual patient, as well as the dosing regimen with the least side effects. Until these medications are systematically studied or newer specific agents are developed for pediatric sleep problems, it is necessary for practitioners looking after children to optimize quality of life and sequalae related to sleep problems, while minimizing potential side effects.

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Assessment and treatment of sleep disturbances in aged population

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Sleep

Sleep is much more than a state of decreased consciousness. It is a phenomenon easy to understand, and at the same time difficult to explain. The science of sleep has been steadily developing over the past 50 years. A number of sleep disorders has been recognized, and different diagnostic tests and treatments have been advanced. In laboratories, sleep is measured by recording various physiological parameters such as electroencephalography (EEG; for monitoring brain waves), electromyography (EMG; for monitoring muscle activity), electrooculography (EOG; for monitoring eye movements) [1]. The respiration and basic cardiac function are also measured, together with various parameters, which are determined by the nature of assessment. Amount of sleep, its composition and architecture changes as we grow and mature. For example a newborn baby may sleep for 16 h during the course of a day, whereas a person in his sixties may habitually sleep only 6 h [2].

Sleep stages

Sleep is basically divided into two major states – rapid eye movement (REM) sleep and non-REM sleep. These two states of sleep differ as much from each other as either of them differ from wakefulness and therefore early in the modern era of sleep research REM sleep was referred to as a "third state of existence [3]. REM sleep is a state of dreaming, increased brain activity and variability in breathing and heart function. At the same time, it is a sleep stage where most of the muscles reach their maximum relaxation. The amount of REM sleep does not change much with aging, and remains stable at around 20 % of total sleep.

Non-REM sleep is divided into 4 stages. Stage 1 represents very light sleep and the person can be easily aroused from this stage. Polysomnographically, this stage is

characterized by low amplitude mixed fast activity (7–12 Hz). In stage 1, sleep there is cessation of alpha activity on the EEG and slow rolling eye movements on EOG can also be observed [1].

Stage 2 represents a stage of consolidation where it becomes more difficult to arouse a person. In this stage, accounting for approximately half of the total sleep time, a person can still be awakened by louder sounds. Polysomnographically, this stage is characterized sleep spindles and K complexes [1].

Stage 3 and 4 are stages of deep sleep and differ only in amount of very slow brain (or delta) waves cycling at 0.5–4 Hz. The amount of deep sleep varies amongst genders and different age groups, and it decreases dramatically from a young age, where it comprises a quarter of one's sleep, to almost nil in males in their seventies.

Sleep in the elderly population

Duration of sleep may decrease as one grows older, but the need for sleep remains the same. There is a high prevalence of dissatisfaction with the quality of sleep among the elderly population and complaints of insomnia are common in this population. Up to 50 % of adults over age 65 have some disruption of sleep and this is confirmed by many epidemiological studies and population surveys [4]. It has been shown that the elderly population has more sleep complaints and uses more hypnotics than the younger people [5]. Sleep disturbances or sleep complaints found in elderly population are often secondary to various medical conditions, including neuropsychiatric disorders, medication use that increases with age and psychosocial factors associated with aging. There is still some question over how much of the change in level of sleep disturbance is as a result of underlying medical disorders and how much is directly related to increasing age. There is also a question of specific physiological changes and the influence these physiological changes in the elderly have on sleep pattern. An example of this is the relation between a menopause and disturbed sleep. Several studies have shown that hormonal changes seen in menopause may independently contribute to sleep disruption, apart from the process of aging [6, 7]. Perimenopausal and menopausal women often report hot flushes disrupting their sleep, which was only partly confirmed with objective testing. In some cases, the complaint is associated with complaints suggestive of sleep-disordered breathing. Most commonly, hot flushes are associated with a complaint of insomnia, with or without depressive symptoms. Different studies have shown variable changes in sleep architecture, including decreased sleep efficiency, high number of partial or complete awakenings, and increased number of sleep-stage shifts [6, 8]. In menopause, treatment of such disruption is not a simple matter. While use of hormone supplement/replacement therapy (HRT) has shown some improvements in perception of sleep quality and, to a small degree, objective sleep parameters, the dilemma of its usefulness remains, compounded by reports of HRT side effects [9–11]. When given to treat sleep disturbances, the combination of low dose conjugated estrogen with micronized progesterone is reported to be most effective [12]. The effect of the HRT should be evaluated once the co-morbid factors, such as depression or sleep-related movement disorders, have been properly managed.

Aging itself invariably brings a change in sleep architecture. A recent meta analysis done by Ohayon et al. [13] showed that elderly individuals have difficulty falling asleep at night, spend more time in bed, have inadequate depth of sleep and experience more awakenings during the night. At the same time, when compared to each other, a prolonged sleep onset was subjectively less of a problem than poor sleep maintenance [14]. Objective sleep studies done in older individuals have shown the following common changes in their sleep pattern [1, 14]:

1. Definite decrease in the percentage of deep sleep (stage 3 and stage 4)
2. Decrease in arousal threshold for noise
3. Reduction in sleep efficiency
4. Increase in sleep latency
5. Mild decrease in REM sleep latency and a slight decrease in the overall percentage of REM sleep.

With the decline in both amplitude of delta waves in the elderly and the enormous percentage decline in slow wave sleep (up to 75–80 %) in the elderly together with what we have referred to as 'endopause' [15], the hormonal changes in sleep of the elderly probably play a major role in the sleep dissatisfaction that the elderly have. Sleep architecture, timing and quality of sleep changes with age. As the total sleep time during the night decreases in the older population, there is often the complaint of excessive sleepiness during the day and increased daytime fatigue, which may lead to daytime napping. This pattern of napping in the older population may contribute to the recent observation that there is less of a difference in the total amount of sleep time required by an elderly person than was previously thought [4]. A study done by Tamaki et al. [16] about effects of daytime napping in the aged has indicated that there is a definite improvement in the behavioral, psychosocial and physiological functions in aged individuals if they take a habitual nap in the mid-afternoon. In general "sleep hygiene rules" indicate that napping is disadvantageous for nocturnal sleep, but this study amongst others indicated that this "rule" cannot be rigorously applied. One possible interpretation of these studies is that there appears to be a regression of sleep patterns in the elderly, with the total sleep time in the 24-h period including more time spent in napping and less time spent in consolidated night sleep than in a younger, middle-aged population. It is not clear as yet in what proportion psychosocial and physiological factors account for these changes.

The primary sleep disorders found in elderly that may lead to sleep disturbances are: (1) circadian rhythm disturbances (CRD); (2) sleep disordered breathing (SDB); (3) insomnia; and (4) restless legs syndrome and periodic limb movement disorder.

We comment briefly on these below. We appreciate that this is far from a comprehensive list but feel it would provide a practical starting point in the management of sleep problems in the elderly. It does not tackle the neurodegenerative disorders that are common in the elderly and which require special attention and consideration. Similarly there are a number of psychiatric disorders that require special attention from a sleep perspective (e.g. , depression) and in which sleep disruption may be both causative and a consequence [17]. Again we see this as beyond the scope of this chapter.

Circadian rhythm disturbances

A biological clock or endogenous circadian pacemaker in a human body is located in the suprachiasmatic nucleus (SCN) in the anterior hypothalamus. It controls various physiological variables such as sleep/wake cycle, and the core temperature cycle on a 24-h basis. This is known as a 'circadian rhythm' [18]. Even though the timing of this rhythm is in part produced intrinsically, it is also influenced by various external stimuli such as light, time of day, social activities and meals [19]. The elderly population tend to loose many of the external inputs that help to synchronize their internal clocks. As a human being ages, the circadian rhythm also becomes internally and externally desynchronized [4].

The most common CRD found in the elderly population is advanced sleep phase syndrome (ASPS) [19]. The complaints of awakening early in the morning and unable to get back to sleep are quite common in the elderly people suffering from ASPS [20]. An older individual with ASPS begins to get sleepy and feels tired in the early evening (around 7 or 8 pm) because of the advanced shift in their sleep/wake cycle. If the individual goes to bed at this time, they may sleep from 9 pm to 3 am and wake up earlier than desired. Individuals suffering from ASPS report excessive sleepiness in the early evening and awakenings in the early morning – the absolute amount of time sleeping is unchanged but the distribution is rearranged. Patients often complain of feeling sleepy during the day in a situation when trying to adhere to a socially cued schedule, which is determined by the amount of sleep deprivation. Aside from the disruption of one's social life, these altered circadian rhythms can be very troubling for caregivers. It can also be very disruptive on family life having parents and grandparents moving around and awake when everyone in the family is still sleeping. This is often viewed as a major reason for institutionalization of the elderly with enormous economic implications [21].

Assessment and treatment

It is sometimes very difficult to distinguish between CRD on the one hand, and insomnia or covert mood disorder featuring primarily increased early morning wake time on the other. Individuals suffering from ASPS may perceive their evening sleepiness as disorder of excessive sleepiness and their early morning awakening as insomnia [4]. Therefore, the identification of CRD is very important to avoid inappropriate or ineffective treatment. The actual diagnosis of CRD can be made not only from patient's history but also from careful mental status examination and with the help of a sleep diary which can give a detail description on patient's time to bed, time spent asleep and awake, daytime functioning and alertness levels throughout the day and night [19]. Wrist actigraphy can also play an important role in diagnosing CRD [4].

Sunlight is considered to be the stabilizer of circadian rhythms thus; the best treatment for ASPS is bright light therapy in early evening or late afternoon [20]. However, the timing for the light exposure is of utmost importance. Studies have shown that two hours of artificial indoor bright light of 2500 lux in the evening is beneficial for ASPS [19]. At the same time, exposure to light in the early morning

hours should be minimal. This shows that a proper timing of light avoidance and light exposure can help stabilize rhythms. Older people should wear dark sunglasses if they go on early morning walks, and should go outdoors in the late afternoon. By regularizing other activities, such as exercise, social activities and wake up times CRD can be improved [19]. Melatonin, a hormone secreted from the pineal gland, also plays an important role in controlling circadian rhythms [18]. Definitely, melatonin has some role to play in the mechanism of both the timing and quality of sleep, as plasma levels of melatonin increases during the night [22]. Melatonin levels have been shown to decrease with age and are reduced by 50 % in older adults at nighttime. It suggests that decrease in melatonin secretion may contribute to poor sleep in elderly patients with insomnia complaints [19, 22]. Research has shown that exogenous melatonin in a proper dose can improve sleep disturbances but proper timing and dose of melatonin administration have not yet been established and this needs further exploration. A study done by Kayumov et al. [23] has shown that melatonin in dose of 5 mg has subjectively and objectively improved delayed sleep phase syndrome without disturbing the sleep continuity and sleep architecture. Some data show that, in case of the ASPS, melatonin should be avoided in the early evening hours, but may be administered after the trough in core body temperature is reached, typically in the early morning hours. Melatonin is also not regulated by the FDA, and hence precaution should be taken regarding the purity and dosage of melatonin sold over the counter [19]. Typically, therapeutic doses range from 0.5–5 mg. While there is evidence of melatonin improving oxidative injury and epithelial recovery, several studies showed that it may cause a worsening of (early morning) asthma [24, 25]. No such studies have offered unequivocal evidence of melatonin worsening cardiac ischemia in humans [26], while there is some evidence of its protective cardiac effect. Other adverse effect of melatonin, such as its interaction with reproductive hormones, is rarely an issue in this population.

Sleep disordered breathing

SDB is characterized by either partial (hypopneas) or complete (apneas) cessations of breathing during sleep. Sleep apnea can be either obstructive (airway collapses and blocks airflow, which may be caused by narrowing at various sites along the upper airway; obstructive sleep apnea, OSA) or central (where respiratory neurons fail to stimulate motor neurons mediating respiration, or respiratory muscles fail to respond; CSA). SDB is diagnosed when a person has a respiratory disturbance index (RDI) ≥ 5; RDI is defined as total number of apneas plus hypopneas per hour of sleep [4]. The cessation of breathing may last anywhere from 10 s to 1–2 min [20], and to resume breathing again the person has to increase respiratory effort, which leads to repeated partial awakenings (arousal) during sleep. The person is typically not aware of these arousals from sleep however, they result in sleep fragmentation and consequent daytime sleepiness.

Symptoms

The cardinal symptoms of SDB are snoring, periodic cessation of breathing (both reported by a bed partner) and daytime sleepiness [4]. Other symptoms include waking with a morning headache, change in mood, nocturnal confusion, dry or sore mouth, nocturia and incontinence. SDB causes sleep fragmentation and daytime sleepiness, which has been associated with an increased incidence of accidents, memory impairment and confusion [20, 27]. If not treated properly, SDB may lead to serious consequences such as elevation in blood pressure, and it results in nocturnal hypertension, cardiovascular disease, problems in concentration, attention and memory during the day [19]. Patients suffering from SDB also often experiences recurrent hypoxemia, which leads to an increased risk of comorbid medical illness, such as systemic and pulmonary hypertension, cardiac arrhythmias, myocardial infarction, and stroke all of which have long-term health implications [4].

Prevalence

The incidence of sleep apnea increases with age. SDB is more common among men than women, and higher among older adults than younger adults. The difference between genders narrows in prevalence after women go through menopause. A conservative estimate of the prevalence of SDB among middle aged adults is estimated at 4 % of men and 2 % of women [28]. A recent study [29] shows that OSA may affect more than 50 % of individuals over the age of 65. One study has shown that prevalence of apnea is higher among African-American group than Caucasians [30]. OSA patients have a high risk of comorbid conditions, such as depression or stroke.

Causes

The common causes of OSA are obesity, enlarged tonsils or large tongue and uvula, narrow airway, jaw deformity as well as a short neck. Other factors like thyroid, pituitary or neurological impairments may also cause OSA. CSA is caused either by increased or decreased responsivity of chemoreceptors and delayed transit of information [4, 19]. In the elderly it is often presumed that laxity of muscles associated with decline in tone is a key factor.

Assessment and treatment

SDB can be assessed based on the combination of various symptoms described by patients such as excessive daytime sleepiness, snoring, cognitive impairment, hypertension, cardiac arrhythmias. Sleep apnea can be accurately and completely diagnosed by referring the patient to a sleep specialist, who takes a detailed sleep history and medical history, followed by a physical examination (neck circumference and configuration of oropharyngeal space is examined) [31]. The gold standard for OAS diagnosis is an overnight polysomnography (PSG) study at the sleep laboratory and daytime sleepiness test (multiple sleep latency test, MSLT), which can

accurately determine the severity and type of apnea as well as the symptom of excessive sleepiness in a patient [27]. Continuous positive airway pressure (CPAP) and Bi positive airway pressure (BiPAP) are the most commonly used and effective means of treatment for OSA [19]. The CPAP system uses a pump that generates positive air pressure. A mask worn over the nose is connected to the pump via a hose. The pump provides constant PAP into the airway and prevents the collapse of the upper airway during sleep. To determine correct air pressure the patient need to undertake a second night of overnight PSG for nCPAP adjustments, called CPAP titration [32]. Once the appropriate CPAP pressure is determined, the use of CPAP helps to eliminate all nocturnal breathing problems and improves oxygen desaturation, and thus reduces sleep fragmentation [31]. A study done by Kribbs et al. . 1993 has shown that even one night without CPAP returns breathing disturbances and daytime symptoms back to baseline. The long-term compliance rate to CPAP is relatively low, and much of this noncompliance is because of various issues such as mask discomfort, nasal dryness, congestion and the white noise of the pressure generator. To improve the daytime functioning and nocturnal breathing, the patient has to show a high level of adherence to CPAP treatment [32]. Oral appliances such as tongue retaining devices (TRD) and other dental devices can also be used in cases of mild apnea. At the same time, most of these need healthy teeth as a support for traction. This is often a problem in elderly patients and therefore less used. Surgical treatments like uvuolpharyngopalatoplasty (UPPP), which involves shortening of the ulva, removal of excessive tissue and tightening of muscles of the oropharyngeal airway can also be used to treat OSA in selected patients [20]. Laser-assisted uvulapalatoplasty (LAUP) is a new surgical procedure in which the surgeon shortens the uvula and trims the short palate with the help of laser, but LAUP is only used to treat snoring [4]. The alternative treatments (dental devices and surgery) are not as successful in all the patients and especially in the elderly population. For overweight patients, weight loss is a good option. Body repositioning during sleep is also very important aspect of a treatment. Lateral as opposed to supine body position has been found to cause lower number of apneic events. CSA is more difficult to treat than OSA. Patients should be instructed to use less sedatives (particularly morphine derivatives) and hypnotics, as well as alcohol, which may exacerbate the apneic events [19]. A treatment of last resort for malignant OSA is tracheotomy, and should be seriously considered in non-responding patients with a serious condition.

Pharmacological treatment of OSA is an elusive concept. A number of selective serotonin receptor inhibitors (SSRIs) and other medications were tried and found to be ineffective. SSRIs and analogous medication have been anecdotally reported to help REM-related OSA, but no study systematically confirmed this claim. Two studies showed positive effect of mirtazapine [33, 34], a tetracyclic non-SSRI antidepressant, on OSA, but further research on a bigger sample is necessary. On the other hand, one should be aware of a muscle relaxation property of some commonly used medications such as benzodiazepines (BZDs), which may result in a worsening of OSA. Assisted nasal ventilation is commonly used in patients with both hypercapnic and non-hypercapnic CSA. The administration of oxygen is observed to ameliorate the frequency of both the central and obstructive events in patients with a predomi-

nantly central component [35] to their apnea. However, use of supplemental oxygen may also worsen patency in patients with prominent obstructive component [36, 37]. A medication that may improve breathing in patients with both hypercapnic and normocapnic [38] CSA is acetazolamide, a carbonic-anhydrase inhibitor. This medication is still not commonly used, partly because of its uncertain long-term effects. The respiratory instability in non-hypercapnic CSA, such as Cheyne-Stokes breathing in patients with congestive heart failure, often responds well to theophylline, a xanthine derivative that is related to caffeine [39]. The use of progestin and other medications that help to stabilize ventilatory response has not been well researched.

Insomnia

Insomnia is associated with difficulty initiating sleep (sleep-onset insomnia), difficulty maintaining sleep (sleep-maintenance insomnia) or awakenings in early morning and difficulty going back to sleep (terminal insomnia) or difficulty obtaining restorative sleep through the night [19]. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), the essential feature of primary insomnia is a complaint of difficulty initiating or maintaining sleep, or non-restorative sleep, that lasts for at least 1 month and causes clinically significant distress or impairment in social, occupational, or other important areas of functioning [40]. Depending on the length of the time the complaint has lasted insomnia can be divided into: (1) transient insomnia, which lasts only for a few days and is caused by a stress related situation; (2) short-term insomnia, which persists for several days to a few weeks; and (3) chronic insomnia, which last from few months to several years and can be a primary problem, but is more often related to long-term psychiatric or other medical conditions [4, 5]. The major complaint of an elderly population is sleep maintenance insomnia and frequent awakenings rather than sleep onset or sleep initiation insomnia. Foley et al. have reported that 49 % of elderly patients experience sleep maintenance symptoms, compared to only 19 % who experiences sleep onset difficulty [41].

Prevalence and consequences

The rate of insomnia is higher among elderly population than in younger adults, one reason being the elderly are much more likely to have chronic medical problems that can severely impact on their sleep quality [4]. Epidemiological studies have found that more than 40 % of those over age 60 complain of disturbed sleep, and over 20 % report severe insomnia [4]. Women tend to complain more about insomnia than men, whereas men are more likely to nap during the day [19]. Studies have also shown that Caucasians had more sleep complaints than African-Americans after controlling all other aspects that may cause insomnia [19]. Quality of life and daytime functioning may be impaired by chronic insomnia. It may also cause cognitive difficulties and mood disturbances, and, in a proportion of patients, lead to daytime sleepiness, which in turn can adversely affect social life and increases the risk of accidents [5, 81]. Older persons with insomnia who live alone are more likely to suffer a fall resulting in major injury than a normal sleeping individual [5].

Causes

Insomnia is rarely found as a primary complaint of sleep disturbance in the elderly population. Insomnia is often secondary to various primary sleep disorders and psychiatric disorders, other medical illness and neurodegenerative disorders. Examples of medical disorders include chronic obstructive pulmonary disease (COPD), asthma and congestive heart failure [42]. Depression is the most common psychiatric condition that causes insomnia. The prevalence of depression in older adults is higher, resulting in sleep disturbances related to depression also being more frequent among the elderly population [4, 42]. Other psychiatric conditions that may cause insomnia in the older population are mood and anxiety disorders [42]. Pain from any source such as arthritis, headache, as well as dyspnea, thyroid disease, diabetes, urinary tract infection and nocturia may also lead to disturbed sleep [42]. Nocturia (the need to void more than five time during the night) is an under-appreciated reason for sleep disruption. The problem of nocturia is twofold – lighter sleep in the elderly makes them more susceptible to waking up because of an expanded bladder, and at the same time, conditions such as benign prostate enlargement in men, and urethral dysfunction in women additionally affect the process of voiding. Nocturia is common in SDB, involving mostly physical mechanisms of change in cavity pressures.

Medication in general may affect sleep. Such an effect is usually amplified in elderly population due to changes in the ability to metabolize active substances. There is a long list of medications that affects sleep, and it includes different groups of psychoactive substances. For example, antidepressant medication such as amitryptiline, mirtazapine, mianserin (used mostly in Europe), doxepin and trazodone causes sedation, whereas bupropion, fluoxetine, sertraline and citalopram may cause insomnia or having an alerting effect. Paroxetine and monoamine oxidase inhibitors predominantly cause insomnia, but do also have reported sedating effects, while venlafaxine, desipramine, imipramine and nortryptiline are reported to cause more sleepiness then insomnia [4]. Medication used in the treatment of bipolar disorders (lithium carbonate, carbamazepine, topiramate, valproate) and some newer antipsychotic agents (clozapine, olanzapine) tend to have a sedating effect (a number of older antipsychotic agents have non-selective sedative properties). Other medications that may cause insomnia include β-blockers (also higher incidence of nightmares), corticosteroids, CNS stimulants, bronchodilators, and pseudoephedrine-based decongestants [4, 42]. Older lipophilic histamine I antagonists have prominent sedative side effects. Alcohol acts as a sedative and shortens sleep latency initially but after a long-term use it causes sleep fragmentation and early morning awakenings. Considering physiological changes, even small amounts of alcohol in the elderly can have a negative impact on sleep [4]. The time of administration and type of medication especially in the elderly that causes insomnia, as well as caffeine intake near bedtime should be taken into consideration to minimize insomnia.

Assessment and treatment

To ensure proper diagnosis and treatment of insomnia, and to rule out other primary sleep disorders, a physician should obtain a thorough sleep, medical and psychiatric

history, and substance use should be noted as well as other medications used, including non-prescription medications [43]. The prevalence of comorbidities, depression in particular, and use of concomitant medication and over-the-counter (OTC) products for sleep problems is very high in an elderly population. One should expect to find a complaint of insomnia underlying a number of psychiatric and medical conditions [43]. Assessment of sleep history should include the questions pertaining to patients' pattern of time in bed, sleep, awakenings, and daytime function [42]. "Fifty-one questions for the elderly insomniac and why" by Shapiro and Steingart [44] gives an example of questions that can be useful in assessing insomnia in elderly population. Physicians should also tell patients to maintain a 2-week sleep diary, which can be a useful tool in assessing patients' sleeping habit [43, 45]. Quantitative information can be obtained from a sleep diary, and knowledge of the time the patient retires to bed, the time taken to fall asleep, the number, timing, and duration of awakenings, and the estimated total sleep time helps in distinguishing between various sleep disorders [2]. Interviewing a bed partner can be helpful in getting more detailed and reliable sleeping and waking habits of the patient [42, 43]. For a comprehensive assessment of insomnia, a brief physical examination and clinical laboratory tests as appropriate should also be included. Physical examination should include vital signs, neck size, and neurological, musculoskeletal, cardiovascular or respiratory problems that may be the primary cause of insomnia. Lab work should include test of vitamin B12 and folate levels as well as test of thyroid function [42]. The objective measurement for evaluating insomnia includes wrist actigraphy and overnight PSG study. The necessity of using an overnight laboratory PSG study in patients complaining of insomnia has been questioned in the past. It is often necessary to rule out other sleep disorders such as SDB or periodic leg movement disorder (PLMD) in cases of persistent insomnia, and this requires a PSG study [4, 45]. There are many patients with sleep "fragmentation" based on repeated brief arousals during the night who have daytime sleepiness. These patients cannot be diagnosed other than by PSG evaluation. There are significant treatment implications, as these patients often respond to prolonged hypnotic usage with dramatically improved quality of life [80]. Physicians can also use questionnaires such as the ESS (The Epworth Sleepiness Scale) and BDI (Beck Depression Inventory) as tools in the assessment of insomnia. Both of these self-administered scales are well validated [43].

Treatment of insomnia

The physician should determine the actual cause of insomnia before prescribing any treatment for insomnia in the elderly population. If insomnia is secondary to an underlying psychiatric or other medical disorder, the focus of treatment should be on those underlying conditions. If any underlying primary sleep disorders or psychiatric and medical condition is present and not diagnosed properly, the treatment recommended may fail and can also exacerbate the problem in elderly population [4]. Increasingly, it is recognized that insomnia needs to be treated in its own right. The quality of life is improved if insomnia is treated and the rate of decline with other disorders, e.g. , multiple sclerosis, end-stage renal disease or rheumatoid arthritis is slowed down

if sleep is improved [82]. The treatments of insomnia are basically divided into two categories: the non-pharmacological and pharmacological treatment.

Non-pharmacological treatment includes various behavioral therapies and cognitive approaches. Sleep hygiene is one of the educational approaches, which includes simple bedtime rules and gives information to the patient in making their daily sleeping habits and environment conducive to a good night's sleep. Some of the instructions given to the patient as sleep hygiene rules are summarized in Tabelle 1 [4, 46, 61]. Stimulus control therapy is a behavioral approach that focuses primarily on shortening sleep onset [4]. In this therapy the patient is instructed to do something relaxing and slightly boring if unable to sleep after about 20–30 min. This process can also be repeated if a patient awakens and cannot fall back to sleep during the night, and thus it can also be effective in sleep maintenance insomnia [46]. Stimulating activities such as watching TV programs, reading exciting books or articles should be avoided. Sleep restriction better termed as "Bed restriction" therapy is another behavioural approach, which helps patients to consolidate their sleep [45]. Many patients with insomnia spend excessive amount of time in bed to achieve sleep and getting no or little sleep leads them to be frustrated and to have anxiety that can eventually perpetuate their sleep problem. Bed restriction therapy instructs the patient to restrict their time in bed equal to the amount of time they actually spend sleeping. This restriction would lead to initial sleep deprivation and thus lead to consolidation of sleep and increase sleep efficiency [4]. Table 2 summarizes some of the instructions given to elderly population under stimulus control therapy. Various other cognitive interventions and group therapy can also be used to improve the quality of sleep among insomniacs. The major drawbacks or difficulties with non-pharmacological treatment include cost, lack of availability, patient motivation and compliance [40]. This non-pharmacological treatment can be used independently or in combination with pharmacological treatment for treating insomnia. Sloan et al. [47] have given an overview of the range of behavioral therapies for insomnia.

Table 1. Sleep hygiene rules for an aged population

1.	Avoid any stimulating activity before bedtime
2.	Do not go to bed until sleepy and reserve it only for purpose of sleeping and sex
3.	Try to keep the bedroom dark, comfortable and quiet which helps you to sleep
4.	Try to keep a regular night bed time and morning wake time
5.	Avoid taking naps, but if any limit them to less then 30 min during the early afternoon
6.	Avoid the use of caffeine, alcohol, tobacco especially after lunch time
7.	Exercise regularly
8.	To increase light exposure spend more time outdoors especially later in the day
9.	A light carbohydrate snack before bed may promote sleep, but avoid eating large fatty meals before bedtime
10.	If unable to sleep, get out of bed and do something boring to take your mind off sleeping

Table adapted from [4, 46, 61].

Note: All these 'rules' should be considered, as 'guidelines' and one at a time should be 'broken' to see if an improvement is obtained.

Table 2. Bed restriction therapy rules for an aged population

1.	The patient should be restricted to bed for the amount of time they think they sleep each night, plus another 15 min. For example, if total sleep time reported by patient is 4.75 h, they are allowed to stay in bed for 5 h but the time should be never less then 4.5 h
2.	The patient must get up in the morning at the same time. If normal awakening time is 6 am, patient must get up at 6 am daily and go to bed at 1 am
3.	Avoid taking naps during the day
4.	Once sleep efficiency has reached 85–90 %, the patient can go to bed 15 min earlier
5.	This procedure can be repeated until patient has achieved desired amount of sleep time

Table adapted from [4, 19].

Table 3. Commonly used BZD and non-BZD hypnotics in treating insomnia

Drug	Recommended dose (mg hs)	Half life (h)	Onset (min)	Duration (h)	Active metabolites
Flurazepam	15–30	50–100	30–60	10–30	Yes
Quazepam	7.5–15	25–40	30	10–30	Yes
Estazolam	1–2	10–24	60–120	10–15	No
Temazepam	15–30	10–17	60–120	8–12	No
Triazolam	0.25	2–4	15–30	2–4	No
Zolpidem	5–10	2.5	30	2–4	No
Zaleplon	5–10	1	30	1–2	No

Table adapted from [2, 5, 19, 20, 31, 61].

The mainstay of pharmacological treatment for insomnia in elderly relies on BZD and non-BZD hypnotics. The age-related changes in an older population regarding issues such as pharmacodynamic and pharmacokinetic parameters, severity of drug-drug interaction, drug accumulation, higher body fat, altered metabolism and decrease in drug excretion makes prescribing a hypnotic a more complex task for a physician in treating the elderly [5]. The intensity of the pharmacological drug response for BZD is quite high in elderly persons compared to their younger counterparts at any given plasma concentration because of the increased sensitivity to BZDs in the elderly population [48]. BZD and non-BZD hypnotics commonly used in older patients for insomnia are listed in Tab. 3. An ideal hypnotic agent is one which has rapid onset of action and elimination, improved ability to initiate and maintain sleep, improves quality of sleep, maintains normal sleep architecture and is devoid of any unwanted side effects. Currently no such ideal hypnotic is available. Many attempts have been made to characterize an ideal hypnotic agent [40]. BZDs are the most widely used medications for treatment of insomnia because of the excellent therapeutic index; however, these drugs may pose a danger of fatal intoxication when combined with other sedatives especially alcohol and CNS depressants [45]. The disadvantage of using BZDs in treating insomnia in older adults is the number of adverse events these drugs can cause, and these include alteration in sleep archi-

tecture (they cause a reduction in slow wave sleep and REM sleep), development of tolerance and dependence following long-term use, memory impairment, motor inhibition, falls and fractures, daytime hangover effects, confusion, apathy, psychomotor retardation, and mild depression of respiratory function. BZDs may also exacerbate coexisting medical conditions, which are more prevalent in older adults; for example, BZD may lead to worsening of sleep apnea or hypoxia associated with certain pulmonary diseases [4, 45, 46]. One of the most important issues related to use of BZD in elderly are falls, injuries and fractures, and most importantly hip fractures. Several studies have shown link between BZD use and increased risk (1.5- to >2-fold) of hip fracture [49]. The higher risk of fracture is associated to high dose, initial use and liver metabolism of a drug, and possibly to a lasting hypnotic effect of an agent [50]. Several studies have reported no such risk association in selected samples, such as hospital wards and nursing homes [51], but after correcting for all of the biases, statistically significant association between BZD and hip fractures still remains [49, 52]. Some of the data suggests that short-acting non-BZDs, such as zaleplon, may provide the necessary safety margin when it comes to residual drowsiness that may impair motor coordination and lead to a fall [53, 54]. In a study [55] comparing other two non-BZD (zopiclone and zolpidem) and lormetazepam, the results suggest that, after a low starting dose (3.75 mg, 5 mg and 1 mg, respectively), zolpidem showed least effect in terms of the motor imbalance and memory loss. Another problem affecting use of BZD hypnotics in elderly patients is the overlap of cognitive symptoms. It is often difficult to judge to what proportion the cognitive impairment in a patient who suffers from dementia, depression and insomnia treated with BZDs is attributed to each of these factors. Use of BZDs, in this case, may both confound the cognitive impairment and mask the symptoms of depression, making it difficult to tailor the treatment protocol. In addition, most of the institutionalized patients receive multiple medications that may amplify cognitive impairment [56].

Elderly patients also suffer from decreased ability to metabolize active ingredients, thus increasing their serum concentration above the optimal therapeutic levels. This is further exacerbated in patients with liver failure or neoplasm [57]. Adverse effects have been reported both with BZDs and non-BZD [58, 59], warranting careful adjustment of the medication regimen. This is more important in polypragmasic patients using medications which compete for the same metabolic mechanisms and in patients with impaired hepatic metabolic clearance. Appropriate selection and dosing of a BZD is very important. Longer acting BZD (flurazepam and quazepam), which have active metabolites produce greater daytime symptoms of sedation, diminished attention, and decreased performance in older adults [45]. Triazolam inspite of being a short-acting BZD has a unique adverse event profile, and thus is not an ideal agent in treating insomnia. Triazolam causes side effects such as confusion, agitation and impaired psychomotor performance, greater degree of sedation, daytime anxiety during treatment and rebound insomnia following discontinuation. These side effects are troublesome in older patients [5]. These side effects in the elderly population are contributed to by a lower clearance rate and higher plasma concentration of triazolam rather than from an increased sensitivity to the drug [60]. Thus, an intermediate-acting BZD like temazepam and oxazepam or zopiclone (a non-BZD) are the choice of medications in treating insomnia in an elderly population since they

also help in treating sleep maintenance insomnia, which is a common complaint in elderly population [4, 27]. Non-BZDs, such as zolpidem, zaleplon and zopiclone, have selective affinity for the BZD receptor subtype 1, and thus have fewer side effects and are rapidly eliminated [5]. Non-BZD hypnotics do not appear to produce as much tolerance and dependence when compared to BZD [5]. Zolpidem is well tolerated and mainly prescribed for sleep onset insomnia. The common adverse events caused by zolpidem are gastrointestinal upset, headache, somnolence, dizziness or light headedness [5]. Zaleplon is prescribed for transient and chronic insomnia, and it can also be used for middle of night awakening 4 h from rising time, and it does not cause residual daytime sedation. The most common adverse event associated with zaleplon is headache [5, 46]. Zopiclone has hypnotic properties equal to or superior to BZD, and its useful in patients who have difficulty falling or staying sleep [46]. The newer non-BZD hypnotics (zolpidem, zaleoplon, and zopiclone) have the advantage of causing less slow wave sleep and REM suppression. BZDs and newer non-BZD hypnotics are much safer than barbiturates are more effective than sedative antidepressants, and are more potent than OTC products [61].

Other medications

Diphenhyradmine has been used to promote sleep, but antihistamines have a drawback of low sedative potency, slow onset of action and high anticholinergic effects [45]. At the same time, data [62] showed that, in the elderly population, the sedative potency of diphenhydramine nearly equals that of BZDs, but with the comparable level of psychomotor impairment. Antidepressants such as amitryptyline, doxepin, mirtazapine and trazodone with sedative effects are increasingly becoming a first choice of treatment among physician for treating insomnia [45]. Tricyclic antidepressants (TCAs) such as amitryptyline, doxepin can cause side effects such as orthostatic hypotension, cardiac arrhythmias, and other anticholinergic side effects. Trazodone and mirtazapine have lower incidence of side effects than TCAs [5].

Trazodone and, increasingly, mirtazapine appear to be frequently used in clinical practice to treat patient with insomnia with secondary (or secondary to) psychopathology. Aside from exhibiting high potency in improving sleep, mirtazapine can cause significant psychomotor impairment when compared to SSRIs, and this should be considered in the situation where there is a need to operate a motor vehicle [63–65]. Since mirtazapine metabolism relies on cytochrome P450 mechanism, caution should be exhibited in patients with impaired hepatic function. There is also a possibility that mirtazapine may induce increased nocturnal movements and REM sleep behavior disorder [66]. Trazodone has a less well-documented track record in improving symptoms of insomnia, with side effect similar to those of mirtazapine (sedation, drowsiness, dizziness, psychomotor impairment) [67]. At the same time, it may serve as an adjuvant treatment in patients with depression and insomnia, in combination with SSRIs [68]. There is a large discrepancy between a surge in use of the OTC herbal medication, and the hypnotic potency of such preparations. Nevertheless, almost 10 % of (younger) populations resort to using OTC herbal preparations as a sleep aid [69]. The most commonly used preparations as a hypnotic are valerian root and kava, and to lesser degree (for this indication), St. John's Wart. There is no

conclusive evidence that any of these preparations has any significant hypnotic effect in non-toxic doses.

Restless legs syndrome and periodic limb movement disorder

Restless legs syndrome (RLS) is best described as an unpleasant sensation and intense discomfort, mainly in the legs when the person is at rest and during the evening or night. This discomfort that urges the person to move their legs or to get up and walk around to get relief from the discomfort, leads to interference with the patients onset of sleep [70]. PLMD also called as nocturnal myoclonus, is another sleep disorder, which is characterized by periodic extension of the big toe and foot that may or may not be related with the flexion of the ankle, knee and sometimes the hip. These rhythmic periodic movements also known as a jerk or a kick last for about 0.5–4 s and occur at intervals of 20–40 s; they lead to repeated awakenings throughout the night in the elderly population [19, 27, 61, 70]. Both RLS and PLMD contribute to insomnia, nonrestorative sleep, excessive daytime sleepiness, daytime fatigue and restlessness, and impaired daytime functioning in the elderly population. [61, 71, 72]. PLMD is quite common in the elderly population and becomes both more common and more severe with age [19]. Several studies have reported the occurrence of PLMD to be 30–50 % in the elderly in comparison to 5–15 % of the general population [27]. Both these disorders can occur at any age but are most commonly found in the elderly population [61]. Studies and surveys [73] have shown that mild symptoms of RLS and PLMD start early and can be observed in many cases during early adulthood (prior to the age of 20). These features progress with advancing age and can be seen more prominently in the later stages of life [74]. The majority of the patients who suffer from RLS also have PLMD (but the converse is not true). This draws our attention to the fact that there may be a common underlying mechanism between these two disorders [27]. A survey conducted among Canadians [73] through personal interviews reflected the prevalence of RLS-related symptoms increases linearly with age. The exact cause of RLS and PLMD is not clear but both of these conditions definitely involve dopaminergic neurotransmission. There is a documented decrease in the D2 receptor binding in the striatum of the patients suffering from RLS and PLMD [61]. In the elderly population RLS and PLMD can also be associated with other diseases such as iron deficiency (low serum ferritin levels), renal failure, peripheral neuropathy and various other conditions such as rheumatoid arthritis, COPD, and fibromyalgia [74]. Several neurodegenerative disorders such as Parkinson's disease, multiple system atrophy usually occurring in elderly patients can also be the cause of RLS and PLMD. RLS induced by many drugs, such as neuroleptics and other dopamine receptor blocking agents used for sedation, is also responsible for sleep disruption in the elderly [71, 74]. Misdiagnosis is thus common, and in some cases diagnosis may be delayed considerably. The International restless leg syndrome study group (IRLSSG) has recommended minimum diagnostic criteria for diagnosing RLS [75, 76].

Assessment and treatment

The diagnosis of RLS can be made from the patient's history, whereas for PLMD a PSG sleep study, actigraphy or immobilization test can be used [75]. In the case of an impaired elderly person, a detailed history from and of family members and caregivers is considered very useful in diagnosing RLS [74].

Non-pharmacological treatment includes control of stimulants or "aggravating" drugs (e.g. , caffeine, tobacco, alcohol, antihistamines, certain antidepressants), improving sleep hygiene, and regular exercise [61, 75]. It has also been reported that soaking the legs and feet in a warm bath provides relief of RLS in some patients [70]. The mainstay of pharmacological treatment for RLS relies on dopaminergic agonists as the first choice followed by opioids, anticonvulsants and BZDs [77]. The first dopaminergic agent used in treating the nocturnal symptoms of RLS, leading to improved quality of sleep in patients, is L-Dopa and carbidopa, but its use is limited because of its augmentation and rebound side effects with long-term use [61, 77]. Ergot dopamine agonists such as bromocriptine (7.5 mg/night), pergolide (0.5 mg q hs) and cabergoline (2.2 mg/day) are also found to be effective but their use is limited because they are associated with side effects like nausea, fibrosis and cardiac valvulopathy, and toxicity risk is also high with long-term use [61, 77]. A study (PEARLS study [71]) has shown substantial improvement in PLMD and sleep disturbances associated with RLS in patients taking pergolide. Long-term use of low-dose pergolide maintained its efficacy, and was also well tolerated in this study [71]. Non-ergot dopamine agonists such as pramipexole (0.375–1.5 mg/night) and ropinirole (0.5–1.5 mg/night) are more effective and better tolerated than ergot derivatives [61]. However, the use of dopamine agonists have been limited in elderly population due to possible interaction with multiple other medications and due to various side effects like insomnia [61], orthostatic hypotension, nausea, dizziness [74].

Sedation and sudden sleep attacks were described in a small number of patients, but it is not clear whether the DA medication is an instigating or contributing factor. The rebound phenomenon related to use of single evening dose of dopamine agonists is managed by adding a dose to sustain dopamine release, or using a single dose sustained release formula. The RLS augmentation is seen typically at higher doses of levodopa treatment, and involves extension of symptoms in intensity, variety or diurnal distribution. Switching from levodopa to a dopamine agonist usually ameliorates symptoms. Levopoda and dopamine agonists are also associated with higher incidence of nightmares and visual hallucinations, more often in elderly and in particular in neurodegenerative diseases such as Parkinson's disease. It is proposed that the aberrant dopaminergic regulation of the REM sleep plays role in this phenomenon.

Opioids are well tolerated and seem to have a long-term efficacy in the treatment of RLS for the elderly population [74, 78]. Opioids such as propoxyphene (65–130 mg) are useful for mild cases of RLS and PLMD, whereas oxycodone (4–5 mg) and methadone (5–10 mg) are reserved for severe resistant symptoms of RLS and PLMD [61]. A retrospective study by Grewal et al. [79] showed a significant decrease in the number of PLM per hour of total sleep time as shown by pre- and post-treatment overnight PSG studies in patients treated with selegiline (5, 10 and

15 mg). The opioids must be used with caution in patients suffering from sleep apnea because of their ability to cause respiratory depression in patients on long-term opioid therapy [61, 74, 78]. BZD such as clonazepam (0.5–2 mg) (occasionally much higher doses are needed), temazepam (7.5–30 mg) can be used as supportive measures in the treatment of RLS-related insomnia, but should be used cautiously in elderly due to side effects such as confusion, ataxia and sedation [19, 61, 74]. A study by Happe et al. [72] has shown that gabapentin in divided doses of 300–1200 mg/day was effective and well tolerated in the treatment of RLS. Other agents that can be beneficial in elderly population suffering from RLS include supplements of folic acid, and intravenous or oral iron [75]. In conclusion, the elderly cherish their sleep as much as any one else. To provide less than the maximum in effort to resolve their sleep problems is ageism at its very worst. The challenges are considerable, but the rewards in this area are worth the effort.

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Sleep disturbances in Alzheimer's disease

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Summary. Alzheimer's disease (AD) is the most common form of late-life dementia. Significant sleep disturbance is an extremely common complaint in AD, affecting as much as half of clinic-based or community AD cases. Typically sleep disturbance in AD is multi-factorial. The major causes of sleep disruption in dementia include: (1) age-dependent physiological changes that arise as part of normal, 'non-pathological' aging; (2) sleep problems due to medical and psychiatric disorders, and their treatments; (3) primary sleep disorders; (4) poor sleep-related habits and behaviors, often collectively referred to as poor 'sleep hygiene'; or (5) some combination of these factors. The various causes of sleep disturbance in AD are reviewed and 'state-of-the-art' treatments for sleep disturbance in AD are described. Finally, a research agenda is proposed, describing the major research gaps that will need to be filled before a definitive guide to effectively treating sleep disturbances in AD can truly be developed.

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that accounts for approximately two thirds of all dementias worldwide. Recent estimates suggest that between 2 and 4 million older adults in the United States have AD. This number is likely to quadruple over the next 50 years, producing an ever increasing burden on health care systems. AD is typically associated with perturbations in the daily sleep-wake cycle. Significant sleep disturbances are common among patients with AD, affecting as many as half of clinic-based or community cases.

Not surprisingly, many of the same neurodegenerative mechanisms that result in the progressive cognitive deficits seen in AD also contribute to the sleep disruptions seen in this patient population. However, it is important to recognize that sleep can be disrupted for other reasons as well. The major causes of sleep disruption in dementia include: (1) the underlying neurophysiological changes that arise as part of normal, 'non-pathological' aging; (2) sleep problems due to one of many medical and psychiatric conditions, and their treatments; (3) primary sleep disorders; (4) poor sleep-related habits and behaviors, collectively referred to as 'sleep hygiene'; or (5) some combination of several or all of these factors.

For AD patients, sleep disturbance can add a tremendous additional burden to the compromised function and quality of life directly attributable to the dementing

process. For caregivers, disturbances in patients' sleep and nighttime behavior, particularly reduced nighttime sleep time, increased nighttime wakefulness and nocturnal wandering that requires caregiver attention, are a significant source of physical and psychological burden and are often cited as a prime reason for the decision to institutionalize a demented family member. For these reasons, more effective management of sleep disturbances in AD should be a priority for AD treatment research.

The biological bases of sleep disturbances in AD

The sleep disturbances that accompany early stage or mild dementia are quite remarkable in that they appear to be exacerbations of the sleep changes found with 'normal' aging, rather than unique disease-related phenomena. The sleep of AD patients is marked by an increased duration and frequency of awakenings, decreased slow-wave sleep and REM sleep, and more daytime napping. Damage to neuronal pathways that initiate and maintain sleep is the most likely cause of the apparent acceleration of these age-related sleep changes in AD patients. The compromised neural structures affected by AD that also control sleep-wake regulation include: the suprachiasmatic nucleus of the hypothalamus (SCN); the neuronal pathways originating in subcortical regions that regulate arousal and sleep-wake cycles, which include the cholinergic basal forebrain nuclei, the serotonergic raphe nuclei, the dopaminergic nigrostriatal and pallidostriatal pathways, and the noradrenergic locus coeruleus; and the cerebrocortical regions that generate EEG slow wave activity during sleep.

There is considerable evidence that sleep disturbance grows more severe with increasing severity of AD [1]. However, the moderate, or intermediate, stage of the disease is when most other behavioral disturbances, such as agitation and wandering, occur with peak frequency. Shifts in the basic circadian sleep-wake rhythm of dementia patients can be severe, and in extreme cases may lead to complete day/night sleep pattern reversals. In end-stage AD, patients may appear to doze fairly continuously throughout most of the day and night, awakening only for brief periods. However, as of this time there have been no prospective longitudinal studies of sleep in AD, and this remains an important gap in our understanding of both the biology and therapeutics of sleep disturbances in demented patients.

Treatment of dementia with oral acetylcholinesterase inhibitors, currently the standard of care for treating cognitive disorders in AD, and increasingly used by specialists in treating a wide variety of dementing diseases, may improve sleep patterns in some patients. These agents are believed to act by enhancing cholinergic transmission in the brain, and the involvement of both forebrain and brainstem cholinergic nuclei in regulating sleep-wake cycles and arousal forms the rationale for expecting some impact on sleep quality by these agents. While some evidence suggests that these agents may increase REM sleep measures, cholinesterase inhibitors may also, unfortunately, induce insomnia and vivid dreams.

Diagnosis of sleep disturbance in AD

Effective diagnosis and treatment of disturbances of the sleep/wake cycle in AD patients has the potential to reduce or eliminate the distress caused by these disturbances, and as a result delay the need for institutionalization that commonly results from these sleep disturbances. While many AD patients develop significant sleep/wake cycle disturbances, treatment research for these problems has been severely hampered. There is little research to determine which AD patients are at greatest risk for sleep disruption, or even whether significant sleep disruptions make AD symptoms, such as cognitive impairment, more severe. As described below in more detail, there has also very little research into effective treatments for sleep disorders in this population.

These lacks in the research literature can be attributed, at least in part, to deficiencies in the current diagnostic system for identifying sleep disorders and other behavioral disturbances in AD. The Food and Drug Administration's Psychopharmacological Drugs Advisory Committee recently emphasized the need for such a comprehensive diagnostic system. A key point made by this Committee was that behavioral problems associated with dementia (including sleep and circadian rhythm disturbances) are scientifically and clinically valid targets of pharmacological intervention. However, the diagnostic criteria currently available to define such behavioral targets preclude development of FDA-acceptable studies of pharmacological interventions because they do not include the required specific indications for such treatments. Further, current diagnostic criteria in themselves may hinder researchers in their efforts to achieve greater understanding of the epidemiology and pathophysiology of these disorders.

Recently, at the request of the National Institute of Mental Health and the National Institute on Aging, a working group addressed some of these problems by developing a provisional set of diagnostic criteria for defining sleep disturbance in AD. This working group attempted to develop better-defined provisional criteria for sleep disturbances in AD [2]. The provisional criteria are based on the best current understanding of sleep/wake cycle disturbances in the AD patient and are designed to correct the limitations of prior criteria. The working group's hope is that these new criteria will help promote state-of-the-art epidemiological, physiological and, especially, pharmacological and non-pharmacological treatment research on sleep/wake disturbances associated with AD. How widespread acceptance and use of these criteria will be and whether they will have a beneficial impact on research in the area will await the test of time.

Interactions between biological changes and environmental situations

Studies of patients living in institutional settings provide much of the available information about sleep disorders in cognitively impaired patients. Environmental factors that promote circadian dysregulation in dementia patients living in such settings include light, noise, activity schedules, and the needs of staff [3]. Ambient light levels

are typically too low in many congregate care facilities to support natural light-dependent internal rhythms, and noisy conditions, especially during the night, are both common and inimical to sleep. The staffing schedules and timing of specific activities in many facilities caring for demented persons may be driven less by the needs of the patients than by compliance with federal and state requirements governing nursing home operations. Regulatory requirements in general fail to incorporate many of the positive evidence-based practices found to be beneficial for demented residents, focusing more attention on feeding and bathing schedules, injury prevention, and detection of medical problems than on sleep and other issues related to patients' quality of life.

Other causes of sleep disturbance in AD

Population-based studies examining the causes, incidence and persistence of sleep disturbances in AD patients are lacking; consequently, little is known about the risk factors for their development. Therefore, one must look to the literature concerning sleep disturbance in the non-demented elderly and factor this with clinical assessment of individual AD patients to make informed inferences about the AD population in order to arrive at effective treatment interventions for individual patients [4].

Physical illness and related treatments

Many elderly persons, whether demented or cognitively intact, have medical conditions that disrupt sleep. Untreated insomnia and daytime sleepiness have been associated with nursing home placement and mortality. Medically ill older adults admitted to acute care hospitals are particularly vulnerable to sleep disruptions, which appear to be created as much by the various treatments and procedures, unfamiliar routines, and environmental conditions, as by the pain, anxiety, and discomfort associated with their underlying medical condition. Medical conditions especially likely to disrupt sleep are congestive heart failure, chronic obstructive pulmonary disease, Parkinson's disease, gastroesophageal reflux disease, arthritis, and nocturia.

Many prescription, over-the-counter medications and social drugs (e.g. , caffeine, nicotine, and alcohol) can disrupt sleep. However, there are no population-based studies relating insomnia or nighttime waking to specific drug classes. Prescribing information for many psychotropic and other drugs often highlights sleep disturbance as a potential side effect in individual patients. In AD, clinical experience dictates that such potential drug effects should always be considered when sleep is disturbed.

Identifying medical disorders that cause poor sleep, followed by changes in management to optimize results, is typically the best initial treatment approach, but may not be sufficient to completely reverse an associated sleep problem. Simple measures may, however, be highly effective in selected cases. For example, pre-bedtime use of analgesics may greatly improve the sleep of patients awakened by pain at night.

Other possible pharmacological causes of sleep disturbance in the medically ill should also be considered, including high-potency diuretics or drugs with CNS stimulant activity (e.g. ., caffeine, amphetamines, methylphenidate, and newer stimulants)

used too late in the day, and multiple medications with the potential for pharmacokinetic or pharmacodynamic interactions that can affect brain function and sleep rhythms.

Concurrent or complicating neuropsychiatric disorders

Sleep in the elderly may also be affected by psychiatric morbidity. Psychiatric disorders, particularly major depressions, are not only associated with disturbed sleep but can also greatly impact both self-report and objective ratings of sleep quantity and quality [5]. Depressive symptoms are common in older adults, especially among persons who are medically ill, bereaved, or cognitively impaired, but by no means always associated with disrupted sleep. In AD patients seen in clinical psychiatric settings, rates of major depression as high as 86 % have been reported, but the majority of studies report more modest rates of 17–29 %.

Depression should always be evaluated as a possible contributor to the sleep disturbances encountered in demented individuals. Pharmacological treatment of mood or behavioral disorders associated with sleep disturbances in AD frequently improves sleep patterns [6], although controlled clinical trials focusing specifically on this dimension are lacking. In psychotic or severely agitated or aggressive patients, antipsychotics are frequently the drugs of choice. Atypical antipsychotic agents with low potential for causing extrapyramidal signs and symptoms are preferred.

Primary sleep disorders

In addition to the sleep disturbances that result from normal aging or brain disease, sleep quality may be impaired by primary sleep disorders, some of which occur with increasing prevalence with age. Sleep disordered breathing (sleep apnea), restless legs syndrome (RLS) and REM sleep behavior disorder (RBD) are three such primary sleep disorders that are more prevalent in older adults.

Sleep apnea syndrome is characterized by the repeated cessation or significant diminution of breathing for 10 seconds or longer, resulting in multiple episodes of hypoxemia multiple brief awakenings, complaints of excessive daytime sleepiness, and impaired daytime functioning. Major risk factors include male gender and obesity. Sleep apnea should be considered in the differential diagnosis when older adults report poor sleep and when cognitive impairment is discovered for the first time. It has been observed that 24–62 % of community-dwelling older adults have sleep-related breathing disturbances, although the true clinical implications of these observations are unclear.

Treatment of obstructive sleep apnea includes behavior modification to minimize sleeping on the back, weight loss for obese patients, avoidance of respiratory depressant drugs (hypnotics and alcohol), oral appliances, such as mandibular advancement devices (MADs) and use of nasal continuous positive airway pressure (CPAP). Apnea is also treated with a variety of surgical interventions including tracheostomy, although these approaches are typically not first-line treatment and carry significant morbidity and mortality risk. For most cases of clinically significant ob-

structive sleep apnea, CPAP remains the treatment of choice. However, adherence to CPAP can be problematic, particularly in demented patients; those with significant cognitive impairment may be unable to understand the value of treatment or learn to use or tolerate it, and nocturnal confusion may lead to automatic removal of the device.

RLS is characterized by a very strong pre-sleep urge to move one's legs and is often described as an 'pulling', 'searing' or 'crawling', which often leads to significant sleep onset insomnia. RLS have been successfully treated with benzodiazepines and opiates; however, dopaminergic agents are the current treatment of choice.

RBD is characterized by a relative absence of the atonia characteristic of REM sleep. This lack of atonia permits the physical acting out of dream mentation, particularly dreams involving confrontation, aggression and violence. RBD is seen most frequently in older men. RBD occurs in both acute and chronic forms. Acute RBD can occur during withdrawal from alcohol or sedative-hypnotics. RBD has also been induced by the tricyclics, SSRIs and venlafaxine. The chronic form of RBD may occur as part of an identifiable underlying neurological disorder, but typically is idiopathic. RBD may also be an initial manifestation of parkinsonism. RBD is very responsive to clonazepam, although this use has not been FDA approved.

Although it might be expected that the incidence of the primary sleep disorders would increase in demented patients relative to age-matched controls because of the CNS dysfunction underlying these disorders, studies comparing the rates of sleep apnea in dementia patients and aged controls have not found consistent differences. Nevertheless, these conditions may interact with the dementia syndrome to further worsen sleep quality as well as cognitive and functional abilities. For example, some studies have shown that sleep apnea is associated with increased morning confusion in AD patients.

Symptomatic treatment of insomnia in AD patients

When insomnia is not caused by, or fails to respond to treatment for, another medical or psychiatric condition in dementia, pharmacological treatment with sedating agents may be considered as symptomatic therapy. Controversies regarding the use of sedating medications in demented patients revolve around issues of efficacy and issues of potential toxicity, neither of which have been resolved by appropriately comprehensive empirical study. There is evidence, however, that sedative-hypnotics as a class may be inappropriately prescribed or overprescribed for demented patients.

Several recent studies have now shown that use of prescription drugs does not necessarily improve subjective and objective ratings of sleep quality in community-dwelling or institutionalized older patients. However, no controlled clinical trials have evaluated the efficacy or toxicity of benzodiazepines or the newer non-benzodiazepine, imidazopyridine hypnotics, such as zolpidem or zaleplon, in groups of demented patients. The hazards of excessive sedation for patients with dementia, including increased impairment in cognition, gait, and balance, and the consequent risk of falls, have been widely publicized but have been surprisingly poorly

studied. Presumably, currently available hypnotics of either benzodiazepine or non-benzodiazepine classes are effective at least in part because of diffuse effects on brain activity mediated through benzodiazepine receptors that are widely distributed in the brain, rather than by specific effects on a putative 'sleep center'. Because of this, the common side effects of both classes of hypnotics are part and parcel of their impact on sleep.

There is considerable disagreement in sleep medicine as to whether long-term drug treatment of primary insomnia is effective and safe. If reliable data are sparse regarding the older population at large, they are sparser still regarding the treatment of AD patients. Buysee [7] has recently examined the state-of-the-art concerning pharmacological treatment of chronic insomnia, and has proposed a point of view that may be applicable to studies of sleep in AD. Buysse [7] distinguishes insomnia as a symptom or complaint, from insomnia as a disorder or disease that causes functional impairment. He highlights evidence that otherwise healthy patients with insomnia have significant abnormalities in physiological function beyond the domains of complaint and sleep reduction. He develops an approach to insomnia that calls for development of neuropsychobiologic models of insomnia, a reliable and valid nosology, and a sequential program of intervention research beginning with non-pharmacological treatments followed by drug therapies for non-responders. This view provides a useful framework not only for insomnia but also for understanding and treating sleep disorders in patients with AD.

The need for controlled clinical trials for improving sleep quality in AD

The absence of controlled clinical trials of symptomatic treatments for insomnia in demented patients represents a serious and continuing gap in knowledge. A recent exception to this absence is the recently completed multi-centered trail of melatonin to improve sleep in AD patients. Based on some promising preliminary results pointing to melatonin's potential efficacy in this arena, the Alzheimer's Cooperative Study, a NIA-funded consortium of AD research centers around the country, undertook the first large, multicenter trial of a sleep therapy in AD patients, specifically melatonin. One hundred fifty seven subjects with AD and sleep disturbance were recruited at 36 different sites and randomized to placebo, 2.5 or 10 mg melatonin and monitored continuously for 2 months by wrist actigraphs. Melatonin failed to improve sleep quality in these severely sleep-disturbed AD patients [8]. Based on this and other recent reports that found little beneficial effect of melatonin on either sleep or agitation in severe AD patients, it appears that melatonin is not particularly effective across the broad range of sleep disturbance in AD.

While the results of this trail were negative, it is nonetheless noteworthy, not only for providing comprehensive data indicating that melatonin is inappropriate for managing sleep disorders in AD patients, but also as an exemplar of exactly the type of trails that are necessary if efficacious evidence-based treatments are to be developed.

Nonpharmacological approaches to treating sleep disturbance in AD patients

In situations where a sleep disturbance is not wholly the result of age-related sleep change, a primary sleep disorder, a specific medical or psychiatric disorder, or a complication of dementia, sleep may become chronically disrupted through the development of poor sleep habits, conditioned emotional responses or poor environmental conditions [9]. These problematic habits and responses interfere with normal regulatory sleep mechanisms and may serve as inhibitors to sleep. A number of behavioral and environmental modification strategies, including sleep hygiene, sleep compression, relaxation training, stimulus control, and multi-component cognitive-behavioral therapy have proven effective for enhancing sleep in older adults without dementing diseases, and some of their components can be helpful in demented patients [9, 10]. There is also an emerging body of literature indicating that light and exercise may also have beneficial impact on sleep quality in both the healthy elderly and demented patients [11].

Overall there is good evidence that non-pharmacological treatments can improve sleep quality and reduce sleeping medication use in older adults. Further, there is emerging evidence that similar non-pharmacological approaches can work as well with AD patients. For example, a colleague has recently reported preliminary data demonstrating that a behaviorally based intervention incorporating sleep hygiene, exercise and light exposure can be successfully implemented in AD patients [12], and may have positive treatment effects on the sleep quality of both AD patients and their caregivers [13]. However, considerably more data like this will be necessary before the practicing physicians most often responsible for treating AD patients start to recommend such nonpharmacological treatments as a first order intervention.

Conclusions and a view to the future

Effectively evaluating and treating disturbed sleep in an AD patient requires an appreciation of the many ways that sleep can be disturbed in such individuals, and the willingness to parse what those casual agents might be and marshal the most effective treatment for each of them. Accurate assessment of sleep disturbances in demented patients can only be done in the context of associated medical disorders, current drug treatments, psychopathology, primary sleep disorders, and behavioral and environmental conditions. Accurate identification of underlying causes, their effective treatment, attention to behavioral and environmental conditions and, where possible, their correction coupled with appropriate and judicious phamacotherapy when necessary, will best address most sleep disturbances in AD patients.

In this review we have attempted to describe the current ‘state-of-the-art’ for understanding and treating sleep disturbance in AD. What is clear is that the literature available to guide such an understanding and to structure effective treatment of sleep disturbance in AD patients is woefully inadequate. It is in this context that we would like to conclude this review with a brief summary (see Tab. 1) of the major gaps

Table 1. Research agenda for future studies of sleep-related issues in AD[a]

1.	Studies that will lead to a better understanding of the longitudinal changes in sleep during the course of dementia, and the impact of those changes on patient quality of life, treatment and care.
2.	Randomized, controlled trials of both behavioral and pharmacological treatments for behavioral disturbances using measures of sleep, daytime function, and impact on caregivers, in addition to behavioral and psychiatric outcome measures.
3.	Randomized, controlled trials to assess comparative efficacy of specific pharmacological and non-pharmacological approaches to improve sleep quality.
4.	Long-term efficacy and safety of newer hypnotic agents in demented patients with sustained sleep disorders.
5.	Studies to provide better understanding of the impact of improved sleep quality on the cognitive and possibly the physical function of demented patients.
6.	Empirical validation of diagnostic criteria and algorithms for assessing and managing sleep problems in dementia.
7.	Controlled health services trials of effect of changes in institutional policies effecting the patient milieu, such as staffing, lighting, organized patient activities, medication protocols, etc., on the sleep of institutionalized dementia patients.

[a] Modified from [14].

in the clinical research literature that will need to be filled before a more definitive guide to treating sleep disturbances in AD can be developed. We trust this list will help guide future research.

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Sleep disturbance during menopause

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Introduction

Sleep disturbances during menopause are either caused by the menopause itself or just co-inside the menopausal period. The clinical picture of menopausal insomnia is indistinguishable from common insomnia, which is a nonspecific complaint of trouble falling asleep (long sleep latency), difficulty staying asleep (excessive or prolonged awakenings), awakening involuntary too early in the morning, or feeling nonrestored from sleep [1, 2]. The adverse consequences, such as fatigue, sleepiness, irritability, mood disorders, memory troubles, lack of concentration or disability in daytime functioning [3] of this poor-quality sleep are similar in menopausal women as in the population in general, and may mimic climacteric symptoms. The same woman may suffer from some or from all insomnia forms.

Menopause is an important milestone for the increase of sleeping problems, especially insomnia. The impact of menopause, however, has yielded various estimates when using subjective methods, like questionnaires, or objective measures, such as polysomnography. In a questionnaire study with over 12 000 participants, both men and women, 15 % of women over 50 years suffered from severe insomnia, whereas only 5 % of women aged 18–24 years reported the same [4]. In men the corresponding numbers were 8 % and 2 %. In a large study including pre-, peri- and postmenopausal women [5] odds ratios for trouble sleeping were 1.6 for postmenopausal and 1.3 for perimenopausal compared to premenopausal women. However, studies assessing sleep by objective measurements have shown little if any specific changes brought about by menopause [6–8]. Furthermore, when comparing postmenopausal women to premenopausal women the objectively measured sleep quality has been found to be similar [9] or even better [10].

Whether sleeping problems in menopausal transition are based on decreased sex hormone levels or solely on aging or on both is not known. In both genders aging has various deteriorating effects on sleep, i.e. , through neuronal loss and atrophy, neurotransmitter defects and decreasing cerebral blood flow [11]. On the other hand, sex hormone receptors, especially estrogen receptors, have been found in brain areas responsible in sleep regulation [12]. By its action, for instance, via several neurotransmitters, sex hormones could influence sleep [13]. Climacteric symptoms are

the most apparent consequences of decreasing sex hormone levels. Those symptoms have clearly been shown to go together with worse subjective sleep [7]. Furthermore, when associated with anxiety, depression, stress and tension, they may cause or at least contribute to sleep problems [14, 15]. In addition to these, sleep-disordered breathing is regarded a primary cause of sleep disturbances during menopause.

Characteristics of climacterium

The end of cyclical development of follicles in ovaries is not abrupt, but is often heralded by years of irregularities in menstruation and gradual changes in other endocrinological and biological functions, including central nervous system (CNS) [16, 17]. The moment when menstruating ceases is menopause. The age range for natural menopause is from 45 to 55 years with an average age of 51–52 years [18]. Perimenopause is the period of time from the first signs of approaching menopause until 12 months of permanent amenorrhea, when the exact time of menopause can be determined. Accordingly, menopause is a retrospective diagnosis. Postmenopause starts when menopause is diagnosed [19]. Climacterium encompasses the perimenopause and the part of the postmenopausal period during which climacteric symptoms occur. Alterations in several other hormones, including an increase in follicle-stimulating hormone (FSH) and luteinizing hormone (LH) and a decrease in inhibin, androgens and prolactin also take place [16].

During climacterium women encounter a number of symptoms with large variation in severity. Vasomotor instability, hot flashes and sweating, are the most typical symptoms with characteristics of thermoregulatory phenomenon: peripheral vasodilatation especially around the face and the chest, which usually is followed by sweating causing evaporative cooling [20]. Although not well established, these symptoms are supposed to mediate through the preoptic area of the anterior hypothalamus. Freedman and coworkers [21, 22] conducted studies with core temperature measurements and concluded that vasomotorically symptomatic postmenopausal women had lower sweating temperature threshold and higher shivering threshold compared to asymptomatic women. However, despite of these findings the detailed background and reasons for variability in symptom frequency and response are uncertain.

Other climacteric symptoms include disturbances in the menstrual pattern, palpitation, headache, dizziness, numbness, myalgia, vaginal dryness and urinal tract symptoms. In over half of the climacterically symptomatic women also mental symptoms, such as anxiety, depression, decline in libido, lack of concentration, and memory impairment, are present; these can exceed the severity of vasomotor symptoms. Further, sleeping problems are frequent during menopausal transition. They may show as exclusive symptoms or in addition to other climacteric symptoms. They are often attributed to nocturnal vasomotor symptoms. In menopausal women vasomotor symptoms are reported in 65–85 %, mental symptoms in 50–80 % and sleeping problems in 50–80 % [23, 24]. The duration of the symptoms has a wide variety. Vasomotor symptoms are experienced for 1–2 years in most of the women, but about 25 % will experience them for 5 years and even 9 % practically all lifelong [25, 26].

The effect of female sex hormone on the brain

Female sex steroids, estrogen and progesterone, have several potent actions in the brain. Thus, they presumably do not only regulate reproductive behaviors but also control a multitude of brain functions, including sleep, cognitive performance, mood, movement co-ordination and pain [27–29].

In the brain, estrogen acts via both nuclear (genomic) and non-nuclear mechanisms. Typical for a nuclear effect is slow initiation and long duration. At least two estrogen receptors, ERα and ERβ, are engaged. Steroid receptors are located in several brain areas, such as in cortex, hippocampus, hypothalamus, amygdala, basal forebrain, midbrain raphe nuclei, pituitary gland, locus coeruleus and cerebellum [30, 31]. Non-nuclear mechanisms include an increase in excitability of neurons, activation of intracellular signaling pathways, modulation of proteins and protection against neuronal damage [30]. The non-nuclear receptor mediated responses are faster and shorter than the nuclear responses.

Sex-steroid hormones affect neuronal transmission in many ways. Neurotransmitter systems such as cholinergic-, serotonergic-, dopaminergic-, adrenergic-, as well as glutamate-, GABA-, opiate- and vasopressin-systems are involved. Also, insulin-like growth factor 1 (IGF-1), transforming growth factor alpha (TGF-α), cyclic AMP, protein kinase activators and various other neurotransmitters can activate estrogen and progesterone receptors. Furthermore, estrogen may restore CNS-related circadian hormones, like growth hormone (GH), glucocorticoid, prolactin or melatonin [32].

While the effects of estrogen on brain function have been intensively studied in humans, the effects of progesterone as a neurosteroid are less well described. The sedative actions of progesterone are documented in both animals and humans [33]. Progesterone has also been shown to have respiratory stimulant properties [34, 35].

Sleep and climacteric symptoms

In all age groups women report sleep disturbance more often than men [4, 36]. Insomnia is reported by 25 % of women and severe insomnia by 15 % between 50 and 64 years of age; in age group over 65 years the prevalence are 25 % and 16 %, respectively [4]. According to several studies menopausal transition has been shown to be critical for increasing sleeping problems. In a study by Baker et al. [37] perimenopausal women reported more frequent and longer arousals, resulting in significantly less sleep than premenopausal women. Also mood symptoms were more common and associated with or even mediated by sleep disturbance. In a survey with 100 menopause clinic patients nearly 80 % of women complained of insomnia and over 90 % suffered from fatigue. The typical complaints included too early morning awakenings or intermittent sleep [38]. According to the study conducted in 1000 French women, the odds ratio for sleeping problems after controlling for age was 1.5 in postmenopausal women compared to menstruating women [39]. In a study with over 1200 responders in UK, the risk for sleep disturbance was even

higher: 1.5 in perimenopausal women and 3.4 in postmenopausal women compared with premenopausal women [40]. In a more recent multicenter Survey of Women's Health Across the Nation (SWAN) [5] odds ratios for trouble sleeping were 1.6 for postmenopausal and 1.3 for perimenopausal compared to premenopausal women.

Several studies support an association between self-reported sleep problems and climacteric symptoms [5, 7, 23, 41]. An European study with over 5000 women reported an unambiguous correlation between insomnia and vasomotor symptoms [23]. In a more resent study with 12 600 women of a multi-ethnic origin in the USA, an odds ratio for sleeping problems in women with climacteric symptoms was 2.0 compared to asymptomatic women [5].

The previous data about the relationship between objectively measured sleep quality (with polysomnography, actigraphy or quantitative analysis of EEG) and climacteric symptoms is limited. Furthermore, in the majority of the previous studies, the occurrence of climacteric symptoms, especially vasomotor symptoms, have been collected relaying on subjective history of the symptoms preceding the recording night [7, 9, 10] or on subjective sensations during the recording night [9, 42, 43]. Presumably because of the different research techniques the results obtained have been incongruent. Shaver et al. [9] reported longer time in bed and longer REM latency in symptomatic women compared to asymptomatic women. In the study of Erlik et al. [42] hot flashes caused arousals. Three other studies, including a large Wisconsin Sleep Cohort Study, could not characterize any specific abnormalities in polysomnography in connection with climacteric symptoms [7, 10, 43]. The study by Woodward and Freedman [6] was the first one obtaining objective measures of vasomotor symptoms during the sleep recording night. They found that vasomotor symptoms disrupted sleep by causing nocturnal awakenings, increasing sleep stage changes and lowering sleep efficiency. A recent study by the same research group [44] showed, however, that hot flashes disclosed by increased sternal skin conductance did not correlate with objective sleep quality.

The effect of hormone therapy on sleep quality

Hormone therapy (HT) has widely been used to control climacteric symptoms for decades [24, 45]. In addition, it has been found to have preventive action at least for osteoporosis [46]. Because of the side-effects and complications associated particularly with long duration of the treatment and in older women [47], such as increased risk for breast cancer and venous thromboembolic events, the consensus today recommends the use of HT only for alleviation of climacteric symptoms and for as short a time as possible. HT has also been found to be an effective treatment to control menopausal sleeping complaints [24, 45, 47, 48]. In a multicenter study with over 200 women, estrogen (patches twice a week for 6 months) abolished sleeping problems for 95 % of women with complaints [24]. In another study, 4 weeks of treatment (2 weeks of estrogen followed by estrogen+progestagen for the next 2 weeks) led to a significant reduction of sleep disturbance. The duration of the study was 1 year. Alleviation of the vasomotor symptoms were strongly associated with improvement in sleep quality in that study [45].

In a study with both vasomotorically symptomatic and asymptomatic postmenopausal women [48], estrogen facilitated falling asleep, decreased nocturnal restlessness and awakenings, and decreased tiredness in the morning and during the daytime. The degree of improvement in vasomotor symptoms was an important predictor for the degree of improvement in sleep disturbance. However, the subset of women with at least some degree of insomnia in the absence of vasomotor symptoms, also reported improved sleep quality during HT. The same was also evident in a recent large randomized, placebo-controlled study of Women's Health Initiative (WHI), evaluating the long-term effects of HT on the quality of life, where enrolment of the participants excluded climacterically moderate or high symptomatic women [47]. The beneficial results of HT on subjective sleep quality are easily explained in vasomotorically symptomatic women, in whom sleeping problems can be regarded secondary to vasomotor symptoms. As for asymptomatic women, two types of explanation could address these findings. Firstly, women may underestimate or not recognize their symptoms. In that case alleviation of the vasomotor symptoms again plays an important role in improving sleep quality. Secondly, decreased hormone levels associated with menopause may interfere with sleep regulation in the CNS causing sleeping disturbance. By replenishing hormone levels by HT, at least some of these symptoms may be abolished.

The findings about the effects of HT on objective sleep quality have not been as unanimous as subjectively measured sleep quality. The main outcomes in previous studies with healthy women are presented in the Table 1. The two most common findings have been an increase in REM sleep [49–51] and reduction of awakenings [42, 49, 52, 53] during HT. In addition, a decrease in nocturnal wakefulness during the entire night [49, 54] or in the first sleep circles [51] has been reported. Moreover, a shortening of sleep latency [50, 55], an improvement in sleep efficiency [52, 54] and a reduction of the rate of cyclic alternating patterns of sleep [52] have also been reported. In some studies no improvement what so ever have been found [56–58]. In the largest study to date, although observational without the placebo group, the postmenopausal women with HT had worse sleep quality compared to their counterparts without HT, as they had less SWS, more S1 sleep and their sleep was more fragmentized [10].

Because of differences in study design, subject enrolment and administration of the treatment (form, dose and duration) in previous HT studies, the conclusion about the effect HT on objectively measured sleep quality is debatable. The results may be influenced by the inclusion of perimenopausal women instead of postmenopausal women [49]. Also, recruiting both naturally and surgically menopausal women to the same sleep study [50] may cause significant bias not only because of wide age range but because in natural menopause biological changes and clinical symptoms occur gradually, while in surgical menopause a sudden decrease in female sex-hormone production leads to major changes in physiological functions and generally to more severe symptoms [59]. The duration of all prospective studies has been short, from 4 weeks to 7 months, and thus the possible long-term effects of HT remain unanswered. In observational studies [10, 55], which also have gained conflicting results, self-chosen use of HT might have influenced the outcomes. Taken together, women

Table 1. Previous studies about HT effect on sleep polysomnography in heathy women

Author(s)	Study design	Subjects
Thomson and Oswald 1977 [49]	Prospective, placebo-controlled, double-blind	34 perimenopausal women
Schiff et al. 1979 [50]	Prospective, randomized, placebo-controlled, double-blind, cross-over	16 hypogonadal women
Erlik et al. 1981 [42]	Case-control	4 postmenopausal women
Purdie et al. 1995 [57]	Prospective, randomized, placebo-controlled, single-blind	33 postmenopausal women
Scharf et al. 1997 [52]	Prospective, placebo-controlled, single-blind	7 postmenopausal women
Polo-Kantola et al. 1999 [53]	Prospective, randomized placebo-controlled, double-blind, cross-over	62 postmenopausal women
Antonijevic et al. 2000 [51]	Prospective	11 postmenopausal women
Montplaisir et al. 2001 [54]	Prospective, randomized, two group-treatment	21 postmenopausal women
Moe et al. 2001 [55]	Descriptive, cross-sectional, secondary analysis	93 postmenopausal women
Young et al. 2003 [10]	Observational	415 postmenopausal women
Saletu-Zyhlarz et al. 2003 [58]	Prospective randomized double-blind, placebo-controlled, three-arm	49 postmenopausal insomniacs and 22 controls

in general feel marked improvement in their sleep during HT. However, not all data obtained from polysomnographic sleep studies support this improvement.

Sleep-disordered breathing during menopause

In addition to climacteric symptoms, sleep-disordered breathing should also be considered as a proposed mechanism for menopausal sleeping problems. The obstructive

Table 1. continued

Treatment	Estrogen effect	Additional observations
Piperazine estrone sulfate. Study duration 14 weeks.	Decrease of wakefulness and awakenings. Increase of REM sleep.	Estrogen effect on hot flashes, mood or anxiety similar to placebo.
Conjugated equine estrogen 0.625mg/day. Study duration 100 days.	Shorter sleep latency. Increase of REM sleep.	Decrease of serum FSH and vasomotor symptoms on estrogen.
Ethinyl estradiol 50 µg x 4 / day. Study duration 30 days.	Decrease of awakenings.	Decrease of hot flashes on estrogen. No placebo group.
Conjugated equine estrogen 0.625 mg/day + norgestrel 0.15 mg/day (days 17-28). Study duration 12 weeks.	No improvement in polysomnographic parameters.	Decrease of menopausal symptoms and improvement of psychological well-being on estrogen.
Conjugated equine estrogen 0.625 mg/day. Study duration 4 weeks.	Improvement of sleep efficiency. Reduction of cyclic alternating patterns of sleep and awakenings.	Decrease of hot flashes on estrogen.
Estradiol 50 µg/24 h patches or gel 2.5g/day. Study duration 7 months.	Decrease of movement arousals	Decrease of serum FSH and vasomotor symptoms on estrogen.
Estradiol 50 µg/24 h patches. Study duration 4 weeks.	Increase of REM sleep. Reduced time awake during first two sleep cycles.	Decrease of serum FSH and LH levels on estrogen. No placebo group.
Conjugated equine estrogen 0.625 mg/day + either medroxyprogesterone acetate 5 mg/day (MPA) or micronized progesterone 200 mg/day. Study duration 6 months.	Improvement of sleep efficiency and reduction of time spent awake after sleep onset during estrogen + micronized progesterone but not during estrogen + MPA	Decrease of menopausal symptoms and improvement of subjective sleep quality during the both treatments. No placebo group.
Conjugated equine estrogen or esterified estrogen combination.	Shorter sleep latency.	No placebo group. Vasomotorically asymptomatic.
Various compounds, not described in details.	Decrease of SWS. Increase of S1 sleep. More fragmented sleep.	
Estradiol valerate (EV) 2 mg/day + progestogen dienogest 3 mg/day or EV 2 mg/day then open-label phase with EV 2 mg/day + dienogest 2 mg/day. Study duration 4 months.	More fragmented sleep. No improvement in polysomnographic parameters.	49 insomniacs and controls. Improvement in subjective sleep in both phases. No measurements for hot flashes.

sleep apnea syndrome (OSAS) is clinically the most important breathing abnormality during sleep with the incidence in the general population of 1–2 %. OSAS is characterized by repeated episodes of upper airway obstruction accompanied by severe snoring, leading either to an apnea or a marked airflow limitation (hypopnea). The diagnosis of OSAS requires occurrence of daytime sleepiness. Initially based on a clinic population OSAS was considered as a male disease, with male:female ratio of 8:1 [60]. However, the large data set of the Wisconsin Sleep Cohort study [61]

showed that the male:female ratio was only 3:1 and that the prevalence of sleep-disordered breathing in women aged 30–60 years was 9 %. Further, if heavy snoring was considered as a criterion, the ratio decreased to even 1.5:1 [62]. Gislason et al. [63] found a frequency of OSA of 2.5 % when both pre- and postmenopausal women aged 40–59 years were enrolled, whereas in a large study by Bixler et al. [64] with 1000 women from general population, 3.9 % of postmenopausal women had OSAS.

In women, partial upper airway obstruction seems to be a more common nocturnal breathing disorder than sleep apnea. However, because of the lack of consistency in diagnostic tools and criteria, the state is often underdiagnosed. In a study with 63 postmenopausal women, a significant partial upper airway obstruction was found in 17 % of the study population [65]. Characteristic physiological findings are hypoventilation and CO_2 retention. The symptoms resemble those of sleep apnea, like heavy snoring, excessive sleepiness, an irresistible tendency to fall asleep, sweating, morning headache, lack of energy, low initiation capacity, difficulties in concentration, poor memory, and low mental tolerance and may even be interpreted as climacteric symptoms.

Sleep-disordered breathing is caused by several mostly structural, but also physiological reasons. After menopause a redistribution of body fat, especially an increase in the waist:hip and in neck circumference has been shown to be fundamental [61]. Another suggested mechanism is the decrease in female sex hormones, particularly in progesterone [66]. Progesterone is known to have respiratory stimulant properties [34, 35] and an effect on genioglossus tone [67]. Thus, it may protect women from the sleep-disordered breathing until menopause.

Several studies have evaluated whether HT after menopause would be effective as a main, or at least an adjuvant, treatment of the nocturnal breathing problems. In an early study by Pickett et al. [56], high dose of combined HT reduced apnea-hypopnea index (AHI) compared to placebo. Two more recent studies by Bixler et al. [64] and Shahar et al. [68] confirmed the beneficial effect of HT. In contrast, Cistulli et al. [69] could not verify the above findings, presumably partly because they included women using various HT preparations, also plain estrogen, in their study. In a placebo-controlled cross-over study with unopposed estrogen, only little improvement in nocturnal breathing problems was found [65]. Keefe et al. [70] showed in their pilot study that both estrogen alone and combined HT decreased AHI. The different outcomes in these two studies may be explained by the fact that in the study of Polo-Kantola et al. [65], the women were originally healthy and only one woman fulfilled criterion of moderate OSAS, whereas Keefe et al. [70] recruited exclusively OSAS patients.

Block et al. [71] published a study of treatment with relatively high dose of medroxyprogesterone acetate (MPA, 30 mg/day), and showed a decrease in duration of apneas comparing to placebo. Using even higher MPA doses (60 mg/day divided in two doses before the bed time) Saaresranta et al. [72] reported a significantly improved ventilation in postmenopausal women. However, since the studies using HT or progesterone alone are still few and conducted mainly without placebo groups with diverge results, nasal continuous positive airway pressure (CPAP) is the treatment of choice in sleep-disordered breathing.

Other sleep-disorders during menopause

Although menopause is an important initiator for sleeping problems, sleep disturbances may just coincide with the menopausal period. Thus other explanatory factors behind should not be dismissed but evaluated with similar intensity at different periods around menopause. The most important reasons embrace depressive mood, stress, behavioral factors, as well as restless leg syndrome (RLS) and periodic limb movement syndrome (PLMS).

Mood symptoms, especially depression, anxiety and lack of initiative occur more frequently in women than in men [73, 74]. The influence of hormonal fluctuations is plausible, as mood symptoms have been connected to the female reproductive cycle (premenstrual tension syndrome, postpartum depression or climacteric depression). Anderson et al. [38] reported that among climacteric women seeking treatment, the occurrence of depressive symptoms was as high as 70–90 %. Several studied have suggested an association between mood symptoms and sleep disturbance in peri- and postmenopausal women [37, 75]. Sleep quality is sensitive to mood disturbances and in a number of cases it may be the first sign of affected mood. Especially awakening too early in the morning originates typically from a depressive mood.

RLS and PLMS are regarded as elements of the similar clinical features with a difference in timing. Whereas RLS takes place during wakefulness, PLMS occurs during sleep. Characteristics of RLS are unpleasant sensations, typically in the lower extremities, urging movement. In PLMS abrupt and repetitive movements usually last 0.5–5 s with the interval of 5–90 s. There is no consistent gender difference in either syndrome. RLS occurs in 5–15 % of the adult population and PLMS in 30 % between 50 and 65 years, and in 45 % over the age of 65 years. Etiologies include idiopathic with highly genetic basis and secondary forms, like iron, magnesium or folate deficiency, renal failure, peripheral neuropathies and use of drugs, especially CNS stimulants and dopamine antagonists [76]. Because of the antidopaminergic action of estrogen, an effect of estrogen on these syndromes is plausible. However, in a study of 62 postmenopausal women, estrogen therapy showed no effect on the frequency of PLM during sleep [77]. Thus, aging with related degenerative processes in CNS are more plausible in increasing the prevalence of these syndromes than the menopausal state *per se* or female sex hormone levels.

For good sleep quality appropriate sleep hygiene is crucial. A dark, quiet room together with comfortable (often low) temperature and bed is essential. Also avoiding daytime napping, especially long ones, may contribute to improvement of sleep. Behavioral factors, such as refreshing drugs (tea, coffee, some soft drinks and herbal drinks), smoking and alcohol intake may interfere with or cause sleep disruption [78]. In addition to poor sleep hygiene, social issues, such as low income, low education or living alone also predispose for sleep complaints [36].

Treatment of sleep disturbances during menopause

Since the origin of the sleep disturbance and the contributing factors involved are often complex, solving or alleviating those problems is also demanding. In women

with climacteric vasomotor symptoms, the first line treatment for insomnia should be HT. Additionally, women whose insomnia is indispensably related to mood symptoms, benefit from HT [48]. A subset of vasomotorically asymptomatic women may also gain an advantage from HT [48], but among them careful screening for other underlying reasons for sleep problems is crucial. In women over 60 years the vascular side effects of HT may surpass the favorable effects on sleep [47], and thus starting treatment should be considered carefully. In case of contraindications or fears for HT other treatment alternatives, such as antidepressants, selective serotonin reuptake inhibitor (SSRI), gabapentin, dietary isofavones and soy foods, as well as relaxation therapies and improvement of sleep hygiene should be considered, although the effectiveness and safeness of these treatments at least in a long run are still unanswered. In sleep-disordered breathing, nasal continuous positive airway pressure (CPAP) remains the treatment of choice until more information about HT, especially about progesterone, is available.

Conclusion

Sleeping problems are a severe public health problem, imposing a serious burden on the individual and society both medically and economically. Climacterium often causes or worsens sleep disturbances. Thus, effective management already at the acute phase will lead to the best outcome. According to women's own judgment, HT significantly improves sleep quality, although studies using polysomnography have reported inconsistent results. HT can thus be considered as a first line therapy for menopausal sleeping problems, especially if other climacteric symptoms are also present. Part of the sleep disturbances may just coincide with the menopausal period and are thus not of endocrinological origin. Therefore, if no relief during HT has been achieved within a few months, or if symptoms and signs direct on other underlying causes, further medical examinations are warranted.

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Chronopharmacology and its implications to the pharmacology of sleep

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The biological clock

Daily rhythms in plants and animals have been observed since ancient times. As early as the fourth century BC, Alexander the Great's scribe Androsthenes noted that the leaves of certain trees opened during the day and closed at night showing a clear 24-h rhythm. We now know that all physiological, biochemical and molecular functions of living organisms are tightly and reproducibly organized within circadian time, including those responsible for drug distribution, anabolism, receptor binding, bioactivity, catabolism and excretion.

In the 4–5 billion years since the appearance of the earliest living organisms, some ambient features important for respiration and photosynthesis, such as the atmospheric temperature and humidity and the concentrations of oxygen and carbon dioxide, continued to change during the development and progressive spreading of life. In contrast, the daily and periodic alternation of light and darkness originating from the rotation of Earth around its own axis and around the Sun, as well as Earth's gravitational pull and magnetic field, are environmental conditions which have remained essentially constant throughout the evolution of all living forms. Hence, all forms of life, fungi, plants, and animals have evolved mechanisms functionally equivalent to a biological clock.

A biological clock provides the possibility of anticipating, and therefore preparing for events repetitively associated with daily light-dark alternations, and is at the basis of the rhythmic patterns of biological variables. The reliance on the clock is so entrenched in life that forced disruptions of the natural synchrony between the environment and the internal clock is a risk factor for a number of diseases [1, 2].

During the past decade, enormous progress has been made in determining the molecular components of the biological clock. The molecular mechanisms that underlie the function of the clock are universally present in all cells and consist of gene-protein-gene feedback loops, in which proteins can down-regulate their own

transcription and stimulate the transcription of other clock proteins [1–3]. Although anchored genetically, circadian rhythms are synchronized by (entrained) and maintain certain phase relationships to exogenous factors, especially the sleep portion of the light-dark schedule. These rhythms will persist with a period different from 24 h when external time cues are suppressed or removed, such as during complete social isolation or in constant light or darkness [1–3].

Research in animals and humans has shown that only a few environmental cues, like light-dark cycles, are effective entraining agents ("Zeitgebers") for the circadian oscillator. An entraining agent can actually reset, or phase shift, the internal clock. Depending on when an organism is exposed to such an entraining agent, circadian rhythms can be advanced, delayed, or not shifted at all. Therefore, a rhythmic variation under the influence of the Zeitgeber as a resetting factor is involved in adjusting the daily activity pattern to the appropriate time of day.

In mammals, a hierarchically major circadian oscillator is located in the suprachiasmatic nuclei (SCN) of the hypothalamus. This circadian master clock acts like a multifunctional timer to adjust the homeostatic system, including sleep and wakefulness, hormonal secretions and various other bodily functions, to the 24-h cycle. Lesions of the SCN eliminate all circadian-driven rhythms. Inversely, SCN transplants to animals whose own SCN had been ablated, can restore circadian activity rhythms. Every single SCN cell exerts a waxing and waning of the firing rate with a predictable circadian rhythm. Synchronized by paracrine signals the SCN produces an output signal that 'drives' endogenously generated daily oscillations in hormones, sleep/wakefulness, alertness, performance, and many other physiological functions.

The sinusoidal output signal produced by the SCN can be described by its period (cycle length), phase (position in the cycle), and amplitude (range between highest and lowest signal). The output amplitude reflects the 'strength' or robustness of the circadian timing system, which can also be described as the drive to restore homeostasis in response to stimuli or the extent to which circadian behavior is separated into distinct periods of activity and rest within one cycle [1–3].

Circadian rhythm disorders

Among the innumerable periodic changes that underlie and support the overt circadian physiological rhythms, the peak values occur in a characteristic sequence over the day (phase map) in human healthy subjects [4]. Such a sequence and spacing reflects the order and temporal relationships of cause-effect in the normal interactions of the various bodily processes, and is the very indicative of organism's health [5]. Disruption of amplitude or phase of circadian rhythms can be produced endogenously, like that seen in many psychiatric disorders, blindness, circadian sleep disorders or most chronic diseases. On the other hand, phase maps may undergo transitory disruptions when humans are compelled to make a rapid phase adjustment as, for example, after a rapid move to a new geographic longitude or as a consequence of shift work [6, 7]. Under such circumstances the various individual 24-h components comprising the circadian phase map do not reset their phases to the new environ-

mental times at the same rate, and become somewhat displaced in their relations to one another.

The basis of chronopharmacology

Medical chronobiology is concerned with the mechanisms of periodic influences on health and disease. Chronopathology is the study of biological rhythms in disease processes and in morbid and mortal events; most medical conditions are affected by circadian rhythms. Chronopharmacology is the discipline that investigates the effects of a drug as a function of biological time. Traditionally, drug delivery has meant getting a simple chemical absorbed predictably from the gut or from the site of injection. A second-generation drug delivery goal has been the perfection of continuous constant rate (zero-order) delivery of drugs. However, living organisms are not 'zero-order' in their response to drugs. As above mentioned, they are predictable resonating dynamic systems, which require different amounts of drug at predictably different times within the circadian cycle to maximize desired and minimize undesired drug effects (chronotoxicity).

Two concepts must be considered when dealing with day-related changes of drug efficacy: (a) circadian changes in drug bioavailability (chronokinetics); (b) circadian changes in the susceptibility to the drug (chronesthesy). Clinical chronopharmacology (or chronotherapeutics) is the purposeful alteration of drug level to match rhythms to optimize therapeutic outcomes and minimize size effects.

Within the past few years it has become apparent that the liver is a biological clock capable of generating its own diurnal rhythms. As the body's primary defense against metabolic poisoning, and the target of many toxic substances, the liver is continuously exposed to relatively high amounts of ingested drugs or toxins. Being a major organ of metabolism and detoxification of drugs, knowledge of circadian effects on transcriptional activities that govern daily biochemical and physiological processes in the liver is key for pharmacological and toxicological studies. In a recent study, out of 3906 genes evaluated, about 4 % of hepatic genes were found to display a significant effect in their expression levels during the day [8]. Among these genes, a circadian variation in relative expression levels of cytochrome P-450 4a3 and N-acetyltransferase of phase I and phase II categories of drug metabolism was found. Therefore, it is essential to consider time of day effects on drug administration and animal sacrifice when designing and interpreting toxicology studies.

Applied chronopharmacology

Several diseases with established oscillatory rhythm in their pathogenesis have been identified. In the case of asthma, chronotherapy has been extensively studied [9, 10]. Airway resistance increases progressively at night in asthmatic patients [11]. Circadian changes are seen in normal lung function, which reaches a low point in the early morning hours. This dip is particularly pronounced in people with asthma.

Chronotherapies that have been employed for asthma include oral corticosteroids, theophylline and β_2-adrenergic agonists [10].

The chronobiology, chronopharmacology and chronotherapeutics of osteoarticular pain have also been extensively reviewed (e.g. , [12]). Patients with osteoarthritis tend to have less pain in the morning and more at night; while those with rheumatoid arthritis, have pain that usually peaks in the morning and decreases throughout the day. In addition, a number of drugs used to treat rheumatic diseases have varying therapeutic and toxic effects based on the time of day of administration [13]. Chronotherapy for all forms of arthritis should be timed to ensure that the highest blood levels of the drug coincide with peak pain. For osteoarthritis sufferers, the optimal time for a nonsteroidal anti-inflammatory drug such as ibuprofen would be around noon or mid-afternoon. The same drug would be more effective for people with rheumatoid arthritis when taken after the evening meal.

Many of the functions of the gastrointestinal tract exhibit circadian rhythms [14, 15]. Gastric acid secretion is highest at night, while gastric and small bowel motility and gastric emptying are all slower at night [16, 17]. These 24-h rhythms have important implications in the pharmacokinetics of orally administered drugs: at nighttime, when gastric motility and emptying are slower, drug disintegration, dissolution, and absorption may be slower [18]. Suppression of nocturnal acid is an important factor in duodenal ulcer healing. Therefore, for an active duodenal ulcer, the recommended dosage regimen for H_2-antagonists is once daily at bedtime [19, 20].

Cardiac events occur with a circadian pattern. Numerous studies have shown an increase in the incidence of early-morning myocardial infarction, sudden cardiac death, stroke and episodes of ischemia (e.g. , [21]). This is because several functions in the cardiovascular system [blood pressure (BP), heart rate, stroke volume, cardiac output, blood flow] show circadian rhythmicity. For example, the ability of platelet to aggregate increases and fibrinolytic activity decreases in the morning, leading to a state of relative hypercoagulability of the blood [21]. BP is at its lowest during the sleep cycle and rises steeply during the early morning awakening period [22]. In addition, circadian changes in lipid fractions in patients and normal subjects may contribute. A circadian rhythm of hepatic cholesterol synthesis occurs [23], and studies with HMG CoA reductase inhibitors indicated that evening dosing was more effective than morning dosing [24]. The circadian variations of glucose and insulin in diabetes have been also extensively studied, and their clinical importance in the case of insulin substitution has been discussed [25].

In the case of cancer, human and animal studies suggest that chemotherapy may be more effective and less toxic if cancer drugs are administered at carefully selected times that take advantage of tumor cell cycles, while being less toxic to normal tissue [26]. The blood flow to tumors and tumor growth rate are both up to threefold greater during each daily activity phase of the circadian cycle than during the daily rest phase. The chronotherapy concept offers further promise for improving current cancer-treatment options, as well as for optimizing the development of new anticancer or supportive agents [26, 27].

As far as drugs that affect the CNS are concerned, information on their chronopharmacology has been available for a long time. Several chronopharmacological studies were performed on the effects of antipsychotic drugs like reserpine, chloropromazine, haloperidol, tetrabenazine, spiperone and pimozide (for a recent review see [28]). The timing of drug efficacy along the circadian cycle differed among drugs, even when the same endpoints were compared. Moreover, the peak time often varied with the variable measured for a given drug.

Human sleep, its duration and organization depend on its circadian phase [29]. A breakthrough chronopharmaceutical formulation against insomnia that plagues many people would be one that addresses the entire oscillatory cycle of human sleeping process. Anti-histamine preparations (with or without mild analgesics), benzodiazepine receptor agonists, sedating antidepressants, neuroleptics, melatonin, and herbal remedies such as valerian are used for treatment of insomnia. Indeed, pharmacological treatment of insomnia has remained the most widely used for decades, despite concerns about long-term effectiveness, habituation, tolerance, and potential complications, especially in elderly people. Chronic hypnotic exposure can also carry additional risks of physical or behavioral dependence, withdrawal, rebound insomnia, and increased mortality [30].

Since efforts should be made to use drugs with fast onset and short half-lives for sleep onset problems, to reduce adverse daytime effects, chronopharmacological data become important. Many animal studies on the effects on sleep duration of pentobarbital and hexobarbital have been performed [28]. Most of them indicated maximal effects after administration in the latter half of the light span or early dark span. Mortality after librium was higher in mice injected during daily dark period (18:00 to 06:00 h) than during light period, with a peak usually at 24:00 h [28]. This circadian peak in susceptibility has a timing similar to other susceptibility rhythms (e.g. , ethanol, valproic acid or audiogenic seizures) in that all fall into a period of increased electrical activity of CNS. The results of rotarod tests in mice after administration of lorazepam indicated a peak at late scotophase. Differences in acrophase and in amplitude as well as age and dose effects, in the presence of unvaried serum levels indicated that peak efficacy was not due to pharmacokinetics (e.g. , drug absorption, pharmacodynamics) [28]. Among patients whose insomnia difficulties were mostly at sleep onset, short-acting drugs like zaleplon and triazolam might be more suitable, whereas zolpidem, zopiclone, eszopiclone and temazepam can be helpful for wakefulness after sleep onset because of their longer duration of activity.

The time-related variations in drug effects have also been clinically applied to the use of antidepressants. Lofepramine had greater antidepressant effect during a 3-week course of therapy when administered at 24:00 h than when administered at 08:00 or 06:00 h [31]. Likewise, the antidepressant effects of clomipramine during a 4-week therapy varied depending on the time of administration, being more effective at noon than after administration in the morning or evening [32]. In animal studies, fluoxetine suppressed the intake of carbohydrates only when administered in the early dark span but not at other time intervals examined. The timing of food, notably on a diet restricted in calories, can play a critical role in this context and must be taken into consideration both in laboratory and clinical studies [33].

Chronobiotics

Drugs that influence the circadian apparatus are often referred as chronobiotics [34]. The prototype of this type of drugs is melatonin. Melatonin secretion is an 'arm' of the biological clock in the sense that it responds to signals from the SCN, and in that the timing of the melatonin rhythm indicates the status of the clock, both in terms of phase (i.e. , internal clock time relative to external clock time) and amplitude. From another point of view, melatonin is also a chemical code of night: the longer the night, the longer the duration of its secretion. In many species, this pattern of secretion serves as a time cue for seasonal rhythms [35].

Like the effects induced by the external Zeitgeber light, effects by the internal Zeitgeber melatonin are also time dependent. Entraining free-running circadian rhythms by administering melatonin is only possible if the SCN is intact. Daily timed administration of melatonin to rats shifts the phase of the circadian clock, and this phase shifting may partly explain melatonin effect on sleep in humans, or 'chronobiotic effect' [34]. Indirect support for such a physiological role derived from clinical studies on blind subjects, who show free running of their circadian rhythms, while a more direct support for this hypothesis was provided by the demonstration that the phase response curve for melatonin was opposite (i.e. , 180 degrees out of phase) to that of light [36, 37].

Within the SCN, melatonin reduces neuronal activity in a time-dependent manner. In rodents, the effects of melatonin on SCN activity are mediated by at least two different receptors. They are insensitive during the day, but sensitive at dusk and dawn (MT2; causes phase shifts) and during early night period (MT1; decreases neuronal firing rate) [38]. Melatonin secreted during nighttime provides enough inertia to resist minor perturbations of the circadian timing system.

The evening increase in melatonin secretion is associated with an increase in the propensity for sleep [39]. This results from the antagonistic action of melatonin on SCN electrical activity mediated by MT1 receptors. Since SCN plays an important role during late evening to counteract sleep propensity derived from the accumulation of the "sleep debt" (possibly adenosine at the anterior hypothalamus) [40], inhibition by melatonin is instrumental in the "opening of the sleep gates" [39]. A new family of hypnotics (melatonin agonists acting mainly on MT1/MT2 receptors at the SCN) is now being tested in the market [41]. It is interesting that ramelteon (TAK-375), one of these MT1/MT2-selective receptor agonists, was able (as melatonin) to induce sleep and to accelerate resynchronization without affecting learning or memory in rats tested by the water maze task or the delayed match to position task, although diazepam and triazolam impaired both tasks. Neither ramelteon nor melatonin demonstrated a rewarding property in the conditioned place-preference test, implying that MT1/MT2 receptor agonists have no abuse potential. In contrast, benzodiazepines and morphine showed rewarding properties in this test [41].

In blind subjects with free-running rhythms, it has been possible to stabilize, or entrain, the sleep/wake cycle to a 24-hour period by giving melatonin, with resulting improvements in sleep and mood [42]. In normal aged subjects [43].and in demented patients with desynchronization of sleep/wake cycle [44] melatonin administration is

helpful in reducing the variation of onset time of sleep. The phase-shifting effects of melatonin were also sufficient to explain its effectiveness as a treatment for circadian-related sleep disorders such as jet lag or the delayed phase sleep syndrome.

A compelling amount of evidence indicates that melatonin is useful for ameliorating jet-lag symptoms in air travelers (see meta-analysis at Cochrane Data Base [45]). We examined the timely use of three factors (melatonin treatment, exposure to light, physical exercise) to hasten the resynchronization of in a group of elite sports competitors after a transmeridian flight comprising 12 time zones [46]. More recently, we published a retrospective analysis of the data obtained from normal volunteers flying from Buenos Aires to Sydney, or from Sydney to Buenos Aires, by a transpolar route in the last 9 years [47]. Mean resynchronization rate was about 2–3 days. It should be noted that the expected minimal resynchronization rate after a 13-h flight across several time zones without any treatment is 7–9 days.

Alzheimer's disease (AD) patients show a greater breakdown of the circadian sleep/wake cycle compared to similarly aged, non-demented controls. Demented patients spend their nights in a state of frequent restlessness and their days in a state of frequent sleepiness. These sleep/wake disturbances became increasingly more marked with progression of the disease. In AD patients with disturbed sleep/wake rhythms there is a higher degree of irregularities in melatonin secretion [48]. The impairment of melatonin secretion present is related to both age and severity of mental impairment [49]. Loss or damage of neurons in the hypothalamic SCN and other parts of the circadian timing system have been implicated in the circadian disturbances of demented patients [50].

The efficacy of melatonin as a chronobiotic in AD patients is supported by several studies [51–59]. The effect of melatonin was seen regardless of any concomitant medication employed to treat cognitive or behavioral signs of disease [44]. In a double-blind study to examine the effects of melatonin on the sleep/wake rhythm, cognitive and non-cognitive functions in AD type of dementia, it was observed that a 3-mg melatonin dose for 4 weeks significantly prolonged actigraphically evaluated sleep time, decreased activity at the night and improved cognitive function [58].

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Overview of currently available benzodiazepine and nonbenzodiazepine hypnotics

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Introduction

Several facts have been established concerning sleep related to gender and age variables. A healthy young adult (20–29 years old) spends 20–28 % of a night's sleep (7–8 hours) in rapid-eye-movement (REM) sleep, 4–5 % in stage 1 sleep, 46–50 % in stage 2 sleep, 6–8 % in stage 3 sleep, and 10–16 % in stage 4 sleep. Under normal conditions sleep efficiency amounts to at least 95 %; that is, waking amounts to 5 % or less of the total time in bed [1–3]. Sleep state quantities for males and females within the same age range are not significantly different. These sleep parameters, however, can be affected by various factors, resulting in a number of sleep problems, many of which can be treated by currently available hypnotics.

In adults, total sleep time, sleep efficiency, percentage of slow wave sleep (stages 3 and 4), and percentage of REM sleep diminish with age, whereas stage 2 sleep latency, wake time after sleep onset, and percentage of stage 1 and stage 2 sleep increase with age [4–7]. In the 2002 "Sleep in America" poll conducted in the United States by the National Sleep Foundation, telephone interviews were carried out among a sample of 1010 adults of 18 years and older [8]. Thirty-nine percent of respondents reported getting less than 7 h of sleep on week nights. Respondents who tended to sleep less during the week were predominantly males between the ages of 18 and 64, those with children in the household, and shift workers. Thus, the reduction of sleep duration was related mainly to the presence of family or work-related stress. More than one-fourth (27 %) of respondents categorized their sleep quality as fair or poor. A diagnosis of insomnia was made when any of the following symptoms were present: difficulty falling asleep, waking often during the night, waking up too early and not being able to get back to sleep, and waking up feeling unrefreshed. Thirty-five percent of the respondents reported having one or more symptoms of insomnia every night or almost every night. Twenty-three percent of the subjects reported having experienced at least one of the four symptoms a few nights per week. Twenty-seven percent of adults reported that they have snored every night or almost every night.

The respondents with symptoms of insomnia included predominantly females (63 %) aged 18–64 years who were in fair or poor health and experienced daytime sleepiness.

A number of poll respondents either sought treatment or self-medicated for their sleep problems. Fifteen percent of the respondents reported using either a prescription sleep medication (8 %) and/or an over-the-counter (OTC) sleep aid (10 %) at least a few nights per month during the past year to help them sleep. Sleep aids were used predominantly by adult females who mentioned having daytime sleepiness.

Interestingly, older poll respondents, 65 years of age and older (53 % of the sample) who rated their overall health as excellent or very good, and who rarely or never experienced daytime sleepiness considered their sleep as either excellent or very good.

An epidemiological study by Foley et al. [9], in which the frequency of sleep complaints was assessed in over 9000 subjects aged 65 years and older, found that between 23 % and 34 % of the participants had symptoms of insomnia. The sleep disorder was associated with an increased number of physical disabilities, OTC medication use, depressive symptoms, and poorer self-perceived health. The investigators concluded that advanced age generally was not associated with more frequent sleep complaints after adjusting for health status. More recently, Foley et al. [10] performed an epidemiological study of 6800 elderly adults over 3 years to determine incidence and remission rates of insomnia. During the first interview nearly 15 % of the sample reported symptoms of insomnia that were associated with a chronic disease. Depression, heart disease, bodily pain, and memory problems were related to more prevalent symptoms of insomnia. Other conditions, such as arthritis, diabetes, obesity, lung disorders, stroke, and osteoporosis were mainly associated with snoring, sleep apnea, daytime sleepiness, and restless leg syndrome. Among survivors with sleep difficulties during the first interview, 932 no longer complained of insomnia 3 years later, and this was related to the successful treatment of their somatic or psychiatric diseases. The authors concluded that age was not a factor in the remission of insomnia, and that the presence of a sleep disorder may not always be a chronic state in the elderly.

Insomnia: diagnostic criteria

Insomnia is a complaint characterized by difficulty falling asleep (sleep latency of more than 30 min), insufficient sleep (total sleep time of less than 5.5–6 h), numerous nocturnal awakenings, an early morning awakening with inability to resume sleep, or nonrestorative sleep. Common daytime complaints include somnolence, fatigue, irritability, and difficulty concentrating and performing everyday tasks. In addition, subjects with a diagnosis of insomnia are at risk for injury, drowsiness while driving, and illness.

The International Classification of Sleep Disorders [11] considers severity criteria as a guide to be applied in conjunction with consideration of the patient's clinical status. Mild insomnia refers to an almost nightly complaint of an insufficient amount of sleep or not feeling rested after the habitual sleep episode. There is little or no

evidence of impairment of social or occupational functioning. Mild insomnia often is associated with feelings of restlessness, irritability, mild anxiety, daytime fatigue, and tiredness. Moderate and severe insomnia refer to a nightly complaint of an insufficient amount of sleep or not being rested after the habitual sleep episode, accompanied by moderate and severe impairment of social or occupational functioning, respectively. No doubt, the severity criteria may help the clinician to more effectively treat the complaint of insomnia.

Traditionally insomnia has been classified into sleep-onset insomnia, sleep-maintaining insomnia and insomnia with early morning awakening. However, such a categorization could be misleading because the respective patterns are not stable over the course of time. In this respect, Hohagen et al. [12] found that only 51 % of 2512 patients who complained of sleep-onset insomnia at the beginning of the study still reported exclusively problems in initiating sleep 4 months later. The stability of sleep-maintaining insomnia and of insomnia with early morning awakening was even lower (17 % and 45 %, respectively). The low stability of the different patterns of insomnia must be taken into consideration when selecting the most appropriate hypnotic drug for treatment of the sleep disorder. Thus, after a relatively short period of time, ultra-short-acting hypnotics would no longer be effective in numerous patients with an initial diagnosis of sleep-onset insomnia.

The duration of insomnia has been considered an important guide to its evaluation and treatment. Individuals with transient insomnia are normal sleepers who experience an acute stress or situation for a few days (e.g., air travel to a new time zone, hospitalization for elective surgery) that disrupts their sleep. The use of sleep-promoting medication (short-acting agent) and good sleep hygiene tend to resolve the problem. Short-term insomnia is usually associated with a situational stress, often related to work or family life or serious medical illness. This type of insomnia may last up to 3 weeks. However, in some cases short-term insomnia may evolve into a chronic condition. Proper sleep hygiene and other nonpharmacological approaches are appropriate for treating short-term insomnia. However, adjunctive use of hypnotic medication, while providing nonpharmacological interventions, could be necessary. Conventionally, long-term or chronic insomnia has been considered to be that lasting for at least 21–30 nights. Usually, it persists for months or years, and its onset may or may not be associated with an identifiable stressor. When there is no other diagnosable condition directly associated with the chronic insomnia, it is diagnosed as a primary insomnia.

If the insomnia is precipitated or aggravated by another sleep disorder or mental disorder, or if it is due to the direct physiological effects of a substance of abuse or a general medical condition, then the other disorder is termed primary and the insomnia secondary [13, 14].

Primary insomnia includes a number of insomnia diagnoses according to the International Classification of Sleep Disorders, including psychophysiological insomnia and idiopathic insomnia [11]. Psychophysiological insomnia most closely resembles primary insomnia. Individuals with idiopathic or childhood-onset insomnia show a lifelong inability to obtain adequate sleep; there is no evidence of medical or psychiatric disorders that could account for the sleep disturbance. In sleep disor-

ders centers, about 15 % of all insomniacs are diagnosed with psychophysiological insomnia. The prevalence of idiopathic insomnia in its pure form is not known.

Secondary insomnia is the most frequent form of insomnia. The determinants of secondary insomnia can be grouped into the following categories: (1) mental disorders; (2) neurological diseases; (3) medical conditions; and (4) abuse of drug- or medication-induced sleep disorder [15]. A list of major factors is included as Tab. 1.

Table 1. Disorders associated with chronic insomnia

1. **Primary insomnia** (psychophysiological insomnia and idiopathic insomnia)
2. **Secondary insomnia**
   - 2.1 **Mental disorders**
     - Anxiety disorder (generalized anxiety disorder, panic disorder with panic attacks during sleep, post-traumatic stress disorder)
     - Depressive disorder (major depressive disorder, bipolar disorder, dysthymic disorder)
     - Psychosis (schizophrenia and other psychoses)
   - 2.2 **Neurological diseases**
     - Alzheimer's disease
     - Parkinson's disease
     - Sleep-related epilepsy
     - Stroke
     - Sleep-related headache
   - 2.3 **Medical conditions**
     - Cardiovascular diseases (angina pectoris, myocardial infarction, congestive heart failure)
     - Respiratory disorders (chronic obstructive pulmonary disease, sleep-related asthma, interstitial lung disease)
     - Gastrointestinal diseases (gastroesophageal reflux, peptic ulcer disease)
     - Endocrine diseases (hypothyroidism, hyperthyroidism, diabetes mellitus)
     - Neoplastic diseases
     - HIV infection
     - Rheumatic diseases (rheumatoid arthritis, fibromyalgia)
   - 2.4 **Sleep in normal pregnancy and during menopause**
   - 2.5 **Medication-and substance-induced sleep disorder**
     - methylxanthines (caffeine, theophylline)
     - antidepressants (fluoxetine, bupropion)
     - antiepileptic drugs (lamotrigine, ethosuximide)
     - antihypertensive agents (β-adrenoceptor antagonists: propranolol, pindolol)
     - corticosteroids (dexamethasone)
     - psychostimulants (ephedrine, pseudoephedrine)
     - nicotine
     - ethanol

The $GABA_A$ receptor and the mechanism of action of benzodiazepine and nonbenzodiazepine hypnotics

γ-Aminobutyric acid (GABA) is the most important inhibitory neurotransmitter in the mammalian brain and localizes to approximately 30 % of central nervous system (CNS) synapses. This inhibitory neurotransmitter is of particular interest because most therapeutically useful hypnotic drugs work by selectively affecting GABA receptors.

A number of classes of GABA receptors, including the $GABA_A$, $GABA_B$, and $GABA_C$, receptor have been characterized in the CNS of several species, including man. The $GABA_A$ receptor is the site of action of several hypnotic agents, including benzodiazepine, cyclopyrrolone (zopiclone, eszopiclone), imidazopyridine (zolpidem), and pyrazolopyrimidine (zaleplon) derivatives. These different classes of hypnotic drugs modulate GABAergic function through different $GABA_A$ receptor subtypes, defined by the subunits that participate in the receptor assembly. To date seven different classes of $GABA_A$ receptor subunits have been identified: α, β, γ, δ, ε, π, and θ. The α, β, and γ subunits contain multiple isoforms or variants: $\alpha_1 - \alpha_6$, $\beta_1 - \beta_3$, and $\gamma_1 - \gamma_3$. The majority of $GABA_A$ receptors consist of α, β, and γ subunit variants. The α_1 subunit-containing $GABA_A$ receptors are the most widely distributed throughout the brain, followed by receptors containing α_2, α_3, and α_5 subunits. The binding site for GABA, $GABA_A$ receptor agonists (muscimol), and antagonists (bicuculline) is at the interface of the α and β subunits, whereas the benzodiazepine-binding site is located on the α/γ subunit interface [16–18]. Benzodiazepine hypnotics bind relatively equivalently at all $GABA_A$ subtypes (α_1, α_2, α_3, α_5). On the other hand, zolpidem and zaleplon preferentially bind α_1-containing subtypes [19]. Analyses of $GABA_A$ receptors by gene knockout strategies and knock-in point mutations have established that the sedative-hypnotic activity of benzodiazepines, zopiclone, eszopiclone, zolpidem, and zaleplon depends on their predominant affinity for α_1-containing receptors, whereas the anxiolytic effect of benzodiazepine derivatives (diazepam, clonazepam, lorazepam) has been shown to be dependent on the integrity of the α_2 subunit.

Pharmacokinetics of benzodiazepine and nonbenzodiazepine hypnotics

Presently available hypnotic drugs for the treatment of transient, short-term, or chronic insomnia differ significantly in pharmacokinetic properties, including elimination half-life and presence of active metabolites. On the other hand, they have in common short absorption and distribution times. As a result, in most circumstances they induce sleep rapidly. According to their elimination half-life, hypnotics can be divided into short-, intermediate-, or long-acting derivatives.

The benzodiazepine hypnotics midazolam, triazolam, and brotizolam, together with zopiclone, eszopiclone, zolpidem, and zaleplon are short-acting derivatives. The benzodiazepines flunitrazepam and temazepam are intermediate-acting hypnotics,

Table 2. Pharmacokinetic parameters for benzodiazepine and nonbenzodiazepine hypnotics

Drug	$t_{1/2}$ (h)[a]	t_{max} (h)[b]	Time to onset (min)	Active metabolite(s)
Short acting agents				
Midazolam	1.2–2.5	0.3	15–30	No
Triazolam	2.1–6.0	1.0	15–30	No
Zopiclone	3.5–6.0	0.5-2.0	15–30	N-oxide derivative
Eszopiclone	5.0–7.0	1.0	15–30	N-oxide derivative
Zolpidem	2.0–2.5	1.0–1.5	30	No
Zaleplon	1.0	0.5–10	15–30	No
Intermediate-acting agents				
Temazepam	10.0–20.0	1.0–1.5	45–60	No
Flunitrazepam	9.0–31.0	1.0	20–30	7-amino derivative N-demethyl derivative
Long-acting agents				
Flurazepam	40.0–150.0	1.0	30–60	Hydroxyethylflurazepam

[a] *Half-life associated with elimination rate constant (k_{el}).* [b] *Time of occurrence of maximum plasma concentration (C_{max}).*

whereas flurazepam is a long-acting derivative (Tab. 2). Benzodiazepine hypnotics are rapidly absorbed after oral administration, and peak plasma concentrations are attained in 0.3–1 h. Metabolism takes place in the liver, and biotransformation products often have hypnotic activity (Tab. 2). For benzodiazepines, the mechanisms of inactivation comprise hydroxylation, methylation, oxidation, and conjugation to form glucuronides [20, 21].

Zopiclone is available as a racemic mixture. Zopiclone, 7.5 mg administered orally at nighttime, is rapidly absorbed. It has a bioavailability of approximately 75 % and a time of occurrence of maximum plasma concentration (C_{max}) of 1.6 hours [22, 23]. The compound undergoes oxidation to the N-oxide metabolite, which is pharmacologically active, and demethylation to the inactive N-demethyl-zopiclone (Tab. 2). The elimination half-life ($t_{1/2}$) of zopiclone and its active metabolite ranges from 3.5 to 6.0 h [24].

The (S)-isomer of zopiclone (eszopiclone) is now available for the treatment of insomnia. (S)-zopiclone is responsible for the hypnotic effect of zopiclone, whereas the (R)-isomer has no hypnotic properties [25]. Eszopiclone is rapidly absorbed and achieves peak plasma concentrations 1 h after its administration. Its $t_{1/2}$, including the N-oxide metabolite, is approximately 5–7 h [26].

Zolpidem is rapidly absorbed after oral administration. Its bioavailability is approximately 70 %. Peak plasma concentrations are attained 1.0–1.5 h after a single therapeutic dose of 10 mg. The major metabolic routes in man include oxidation and hydroxylation, and none of the metabolites is pharmacologically active. The mean $t_{1/2}$ of zolpidem in healthy volunteers is 2.0–2.5 h [27] (Tab. 2).

Zaleplon is rapidly and almost completely absorbed following oral administration of a 10 mg dose. The compound undergoes significant first-pass hepatic metabolism after absorption. As a result, its bioavailability amounts to only 30 %. The compound attains maximum plasma concentration in approximately 1 h and has a terminal $t_{1/2}$ of 1.0 h. Zaleplon is primarily metabolized by aldehyde oxidase, and all of its metabolites are pharmacologically inactive [28, 29].

Metabolic clearance of benzodiazepine and nonbenzodiazepine hypnotics in populations at risk

Age and disease may affect the disposition of benzodiazepine hypnotics. Such effects are reflected in modifications of the pharmacokinetic parameters, which in turn may influence the clinical profile of the hypnotic drugs [30]. An augmented sensitivity to the effect of benzodiazepine hypnotics is a common finding in aging, especially in patients of 65 years and older. This is associated with a reduced clearance and an increased $t_{1/2}$ of the drugs, which depends upon a change in their volume of distribution [31, 32]. Because of the central role of the liver in the clearance of benzodiazepine hypnotics, hepatic disease leads to impaired removal of these drugs from the body. The clearance of oxidatively metabolized benzodiazepine hypnotics (triazolam, flunitrazepam, flurazepam) is much more affected than of those that undergo glucuronidation (temazepam) [32, 33]. In patients with chronic liver disease, such as alcoholic cirrhosis, and also acute dysfunction caused by viral hepatitis, the reduction of plasma binding with the resultant increase in the total volume of distribution, contributes to the impaired clearance. As a result the mean $t_{1/2}$ is markedly increased (Tab. 3). Renal failure can also affect the pharmacokinetics of benzodiazepine hypnotics. The reduction of plasma binding frequently associated with renal disease is the major causative factor in this type of patient. This results in an increase of the unbound fraction of the drug in plasma. The clearance of benzodiazepine hypnotics that are metabolized by glucuronidation is also affected in renal disease.

Table 3. Pharmacokinetic properties of benzodiazepine and nonbenzodiazepine hypnotics

	Metabolic clearance		
Drug	**Elderly**	**Hepatic impairment**	**Renal insufficiency**
Benzodiazepines	reduced	reduced	reduced in chronic renal insufficiency
Zopiclone	reduced	reduced	reduced in severe renal failure
Zolpidem	reduced	reduced	reduced in chronic renal insufficiency
Zaleplon	not adequately studied	reduced	not altered in mild to moderate renal insufficiency

The metabolic clearance of zopiclone is reduced in elderly patients, aged 65 years and older, resulting in increases in peak plasma concentration and $t_{1/2}$ [34]. The removal of zopiclone from the body is also impaired in patients with liver disease. Reductions in clearance in patients with renal impairment are significant only in severe renal failure [35] (Tab. 3).

Up to the present time no studies have been published on the pharmacokinetics of eszopiclone in elderly patients or patients with hepatic or renal impairment.

In the elderly there is a consistent increase in the maximum plasma concentration and the $t_{1/2}$ of zolpidem. This is related to a reduced volume of distribution associated with a decrease in clearance [36]. As with other hypnotics that are extensively degraded in the liver and show high protein binding, the pharmacokinetics of zolpidem is altered in patients with liver disease. Accordingly, in patients with hepatic insufficiency receiving zolpidem, the C_{max} and the $t_{1/2}$ are consistently increased [36, 37]. In patients with renal insufficiency the disposition rate of zolpidem is decreased compared with that of age-matched healthy adults (Tab. 3).

The pharmacokinetics of zaleplon in elderly subjects is not significantly different from that in young healthy subjects [38]. Nevertheless, Drover [39] contends that this conclusion may indicate a lack of adequate studies in this area. As described earlier, zaleplon is metabolized primarily by the liver and undergoes significant presystemic metabolism. Consequently, the oral clearance of zaleplon is reduced, and the drug effect is prolonged in patients with hepatic impairment [40]. The clearance of zaleplon is not altered in patients with mild to moderate renal insufficiency [40] (Tab. 3).

In summary, based on the available evidence, a reduction in the initial dose of benzodiazepine hypnotics, zopiclone, zolpidem, zaleplon, and presumably eszopiclone, is recommended in elderly patients and patients with hepatic or renal impairment.

The effect of benzodiazepine and nonbenzodiazepine hypnotics on sleep variables in patients with insomnia

Benzodiazepine and nonbenzodiazepine hypnotics are appropriate for transient, short-term, and chronic insomnia [41, 42]. Much of the information on the effect of hypnotic drugs on sleep variables in chronic insomnia has been gathered from studies that included patients with chronic primary insomnia. Notwithstanding this, hypnotic drugs also have been administered for months or years to patients when the appropriate treatment of the underlying disorder (generalized anxiety disorder, major depressive disorder, fibromyalgia, menopause) did not improve the insomnia complaint. Thus, long-term hypnotic medication may be beneficial not only in chronic primary insomnia but also in secondary insomnias, as an adjunct to treatment of the primary disorder [43].

Evaluation of the effect of hypnotic drugs on sleep induction and maintenance in patients with chronic primary insomnia is based on sleep laboratory studies and subjective data from clinical trials. The sleep induced by benzodiazepine hypnotics, including midazolam, triazolam, temazepam, flunitrazepam, quazepam, and flurazepam, is characterized by shortened sleep-onset latency, decreased number of

Table 4. Effects of benzodiazepine and nonbenzodiazepine hypnotics on sleep parameters in patients with chronic primary insomnia

Variable	Benzodiazepines	Zopiclone	Eszopiclone	Zolpidem	Zaleplon
Sleep induction					
Stage 2 sleep latency	Decrease	Decrease	Decrease	Decrease	Decrease
Sleep maintenance					
Number of awakenings	Decrease	Decrease	Decrease	Decrease	No change
Wake time after sleep onset	Decrease	Decrease	Decrease	Decrease	No change
Total sleep time	Increase	Increase	Increase	Increase	No change
Subjective measure of sleep					
Sleep quality	Improv.	Improv.	Improv.	Improv.	No change
Sleep architecture					
Stage 2 sleep	Increase	Increase	Increase	Increase	No change
Slow wave sleep	Decrease	Decrease or no change	No change	No change	No change
REM sleep	Decrease	No change	No change	No change	No change

nocturnal awakenings, reduced time spent awake, increase in stage 2 non-REM sleep, consistent reduction in slow wave sleep, dose-dependent suppression of REM sleep, and improvement in the subjective quality of sleep when compared with no treatment [2, 44, 45] (Tab. 4). Clinical and polysomnographic studies of triazolam, temazepam, quazepam, and flurazepam have found improvement in sleep over 4–5 weeks [46–50]. Thus, benzodiazepines are effective hypnotics when administered over a relatively short period of time in patients with chronic insomnia. Nevertheless, tolerance has not been reported for temazepam and triazolam in some studies [51–53].

Table 5. Dosages of hypnotics used in the treatment of chronic primary insomnia

Drug	Dosage (mg/night)	
	Adult	Elderly
Benzodiazepines		
Flunitrazepam	1	0.5
Temazepam	15-30	7.5-15
Triazolam	0.25	0.125
Midazolam	15	7.5
Nonbenzodiazepines		
Zopiclone	7.5	3.5
Eszopiclone	3	2
Zolpidem	10	5
Zaleplon	10	5

Zopiclone, 7.5 mg per night, is effective in inducing and maintaining sleep in patients with chronic primary insomnia. The increase in total sleep time is related to greater amounts of non-REM sleep (Tab. 4). No significant change has been observed in REM sleep duration as a percentage of total sleep time, although REM latency may be delayed [54–56]. In healthy young individuals, zopiclone decreases stage 1 sleep and increases sleep stages 2 and 3 or stages 3 and 4 combined [57, 58]. However, in adult and elderly patients with insomnia, zopiclone increases, decreases, or has no effect on stage 3 and/or stage 4 sleep as a percentage of total sleep time [24, 59]. No development of tolerance has been observed in studies of zopiclone that lasted up to 4 weeks. The potential for tolerance during longer-term treatment therefore remains unclear [34].

The effect of eszopiclone has been assessed in healthy adults using the first night effect of transient insomnia. Eszopiclone (2.0–3.5 mg) significantly decreased polysomnographic latency to persistent sleep, wake time after sleep onset, and number of awakenings, whereas sleep efficiency was improved [60]. In addition, the efficacy and safety of eszopiclone were characterized across 6 weeks in adults with chronic primary insomnia. Eszopiclone (3 mg) reduced time to sleep onset, increased total sleep time and sleep efficiency, and enhanced quality and depth of sleep. There was no evidence of tolerance or rebound insomnia. Sleep stages 3 and 4 and REM sleep were preserved, whereas stage 2 sleep was significantly enhanced [61]. Krystal et al. [62] determined the efficacy of eszopiclone over 6 months of nightly treatment in adult patients with chronic primary insomnia. Data were collected monthly using an interactive voice response system. Throughout the 6 months eszopiclone (3 mg) improved sleep induction and maintenance with no evidence of tolerance. Thus, the limited available evidence tends to indicate that eszopiclone has similar efficacy on sleep induction and maintenance as that of zopiclone and zolpidem in patients with chronic primary insomnia [42, 55, 56].

In healthy young adults, zolpidem (10 or 20 mg) reduces sleep-onset latency at night and increases total sleep time, whereas slow wave sleep is increased after 20 or 30 mg doses [63]. Polysomnographic studies in poor sleepers and patients with chronic insomnia have shown that zolpidem administered at a dosage of 10 mg at night for 4 weeks significantly increased sleep duration and diminished time awake after the onset of sleep. Stage 2 sleep latency was also reduced. Zolpidem markedly increased the duration of stage 2 sleep without significantly affecting or increasing slow wave sleep [42, 50, 64, 65] (Tab. 4). The duration and latency of REM sleep occurrence were not significantly modified after zolpidem (10 mg) administration [64, 65]. No evidence of tolerance has been observed in long-term (3–13 months) studies whether zolpidem was given on a non-nightly [66] or nightly basis [67, 68].

Quantitative EEG analysis has been used to investigate the effects of zolpidem on delta (slow wave) activity in poor sleepers and chronic insomniacs. Benoit et al. [69] found that zolpidem had little influence on delta activity during nighttime in young individuals with long-standing poor sleep. On the other hand, Monti et al. [70] described an increase in power density in the 0.25–1.0 Hz band during short-term and intermediate-term zolpidem administration in patients with chronic primary insomnia.

Adult outpatients with chronic primary insomnia have been evaluated in studies that compared the effects of zaleplon at doses of 5 or 10 mg with placebo on sleep variables. Polysomnographic and subjective assessments indicated that zaleplon significantly reduced the time required to fall asleep. Estimates of total sleep time and number of awakenings showed no significant differences between placebo and zaleplon (Tab. 4). Zaleplon did not affect non-REM sleep stages or REM sleep [28, 71, 72]. Tolerance to the sleep-inducing effect of zaleplon did not occur in a polysomnographic study by Walsh et al. [72], in which zaleplon (10 mg) was given for 35 nights. However, tolerance to the hypnotic effect of a 5-mg dose of zaleplon developed upon repeated administration [73].

Adverse effects of benzodiazepine and nonbenzodiazepine hypnotics

The commonly reported adverse effects of benzodiazepine hypnotics are drowsiness, tiredness, dysarthria, ataxia, depression, and anterograde amnesia [20, 21]. Memory impairment has been reported more often with benzodiazepines that have short half-lives and a high affinity for the $GABA_A$ α_1 subunit-containing receptors, such as triazolam and midazolam [74, 75]. Daytime functioning can be negatively affected, as evidenced by the effects on measures of psychomotor performance in patients taking long-acting derivatives. In addition, daytime anxiety can occur in individuals receiving short-acting benzodiazepines [21, 76–78]. Increased daytime sleepiness, as quantified by the polysomnographically measured disposition to fall asleep during the day (multiple sleep latency test), can occur. This adverse effect is associated with an increase in the rate of accidents on the road, in the home, and at work [79]. The elderly are particularly susceptible to the adverse effects of benzodiazepines, due to age-related alterations in pharmacokinetics as a result of changes in hepatic metabolism and renal excretion.

Zopiclone exhibits an adverse-effect profile similar to that of the shorter acting benzodiazepines. Hence, poor quality of awakening, drowsiness, tiredness, nightmares, and a dry or bitter taste in the mouth have been reported. The bitter taste is the main reason for treatment discontinuation [80]. Zopiclone also impairs memory and psychomotor performance within the first few hours after administration [77, 81].

The most common treatment-related adverse events during eszopiclone administration are headache, nausea, vomiting and an unpleasant or bitter taste [61, 62]. The unpleasant or bitter taste is prevalent among patients, and constitutes the main reason for treatment discontinuation.

Zolpidem does not impair the psychomotor performance of patients the morning after administration. Adverse effects reported during its administration include dizziness and lightheadedness, somnolence, headache, and gastrointestinal upset. At doses of 10 mg there is no effect on anterograde memory [50, 82].

Adverse events occurring among zaleplon (5 or 10 mg)-treated patients include abdominal pain, asthenia, headache, dyspepsia, nausea, dizziness, and somnolence [28].

Long-term nightly *versus* non-nightly administration of hypnotic drugs in the treatment of chronic insomnia

Presently available hypnotics are effective for the short-term treatment of insomnia. The long-term indication for hypnotic drugs has been discouraged on the grounds of risk of rebound insomnia, a withdrawal reaction, and/or dependence. Strictly, this recommendation applies only to the older benzodiazepines. Notwithstanding this, it has been extended to the recently introduced nonbenzodiazepine hypnotics, which have a very low potential of causing rebound insomnia, dependence, or other adverse effects on health [83, 84]. In this respect, evidence from accumulated clinical practice and controlled studies indicates that long-term pharmacological treatment of insomnia with zolpidem and eszopiclone is efficacious and safe [62, 66–68].

Sateia and Nowell [85] have proposed that long-term treatment with hypnotic medication could be implemented in patients with persistent insomnia not related to mental disorders, neurological diseases, medical conditions, or the effect of a substance of abuse or medication. In addition, nonpharmacological approaches have to be proven ineffective. Circumstances in which the long-term administration of hypnotic drugs must be discontinued include the development of tolerance and dose escalation, the occurrence of severe adverse events, and the diagnosis of newly developed disabilities.

Non-nightly hypnotic administration has been proposed as an alternative option to the nightly drug intake. To date, information on the efficacy and safety of non-nightly intake of hypnotic medication is available only for zolpidem. Administration of zolpidem (10 mg) for 5 nights followed by 2 nights of placebo per week for 2 weeks induced an improvement of sleep that was comparable to the nightly zolpidem treatment in patients with chronic insomnia. Rebound insomnia did not occur on the nights during which zolpidem was substituted by a placebo [86]. In another study nightly and non-nightly zolpidem treatment were compared using the same design except that the two placebo nights per week were randomly assigned. Again, improvement of sleep was equivalent in the two groups of patients [87]. More recently, zolpidem (10 mg) or placebo was administered for 12 weeks to patients with a diagnosis of chronic primary insomnia. The patients were instructed to take no fewer than three and no more than five pills per week. Sleep was evaluated daily with sleep diaries. Patients receiving zolpidem exhibited an improvement of sleep induction and maintenance that persisted over time. There was neither rebound insomnia nor dose escalation [66]. Thus, presently available data tend to indicate that long-term non-nightly administration of zolpidem (10 mg) is an appropriate alternative to the nightly use of the hypnotic drug in patients with chronic primary insomnia.

In conclusion, sleep-related complaints are common in the general population. Prevalence rates are significantly higher among women and the older age groups. Primary insomnia results from the reaction to an emotional trigger or stressful event, which leads to the further development of sleep-preventing associations. Secondary insomnia is that related to another mental disorder, a neurological disease, another sleep disorder, a general medical condition, the effect of a drug of abuse or a medication. In patients with primary insomnia nonpharmacological strategies and sleep-

promoting medication are indicated. In patients with secondary insomnia the underlying disorder needs to be treated appropriately. Notwithstanding, hypnotic medication may be beneficial in secondary insomnias, as an adjunct to treatment of the primary disorder. Currently used hypnotics include benzodiazepine derivatives, the cyclopyrrolone zopiclone, the imidazopyridine zolpidem, and the pirazolopyrimidine zaleplon. In patients with primary insomnia most hypnotics reduce sleep-onset latency, decrease the number of nocturnal awakenings, and reduce the time spent awake. The increase of total sleep time is related to greater amounts of non-REM sleep. Sleep quality is also improved.

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